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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1995

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Departments of Labor, Health and Hu...

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SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

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[1] Died March 29, 1994

PART 4

NATIONAL INSTITUTES OF HEALTH

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1995

HEARINGS

BEFORE A

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HOUSE OF REPRESENTATIVES

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1995

TUESDAY, APRIL 19, 1994.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. HAROLD VARMUS, DIRECTOR
DR. RUTH KIRSCHSTEIN, DEPUTY DIRECTOR
JOHN D. MAHONEY, DEPUTY DIRECTOR FOR ADMINISTRATION
DR. WENDY BALDWIN, DEPUTY DIRECTOR FOR EXTRAMURAL RESEARCH
DR. MICHAEL GOTTESMAN, ACTING DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH
DARYL CHAMBLEE, ACTING DEPUTY DIRECTOR FOR SCIENCE POLICY AND TECHNOLOGY TRANSFER
FRANCINE LITTLE, ACTING DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT
DR. WILLIAM PAUL, DIRECTOR, OFFICE OF AIDS RESEARCH
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

OPENING STATEMENT

Mr. SMITH. This morning we have the overview of the National Institutes of Health, and we are pleased to have with us the Director, Dr. Varmus, and a number of others. You may proceed.

Dr. VARMUS. Thank you.

Mr. Chairman, committee Members, Mr. Porter, I am pleased to appear before you for the first time as the Director of NIH to present the President's fiscal year 1995 budget. I have taken over the NIH at a difficult time, with enormous opportunities to improve the Nation's health. But biomedical research must be balanced against a legislative need for fiscal restraint. This tension between the scientific potential of the NIH and economic reality will surface repeatedly in my remarks.

I would like to begin by describing some of the current excitement in biomedical research. I will then recount several means I have taken to make better use of our research dollars. I will conclude by outlining the components of the President's proposal for fiscal year 1995.

The biological sciences are in a phase of remarkable growth, productivity and promise. New physical and chemical methods are providing detailed visual images of the molecules of life, and these methods are opening a new era in the development of drugs. Molecular biology has revealed the composition and actions of genes, including those genes that predispose us to disease when we inherit them in abnormal form.

Biochemistry is teaching us how our cells respond to environmental cues that govern growth, providing new strategies for the diagnosis and treatment of cancer and other diseases. Neuroscience has revolutionized approaches to the normal brain and to its cells and to chemical signals that flow between them; to disorders of the nervous system; and to cognition and behavior.

Armed with such methods, investigators supported by the NIH have reported many important achievements in the past year that illustrate the potential of NIH to improve the Nation's health. Let's consider just three examples.

First, two genes that strongly influence the probability of developing a common form of colon cancer, diagnosed in over 10,000 individuals in America each year, have been isolated from human chromosomes two and three. It should soon be possible to identify people who have inherited an abnormal form of either of these genes. This will allow early detection of disease by colonoscopy and save many lives each year.

Second, two large-scale clinical studies have changed the standard for the optimal management of diabetes. One study established the value of careful control of blood sugar for preventing the major complications and costs of insulin-dependent diabetes mellitus—blindness and kidney failure. The other has shown that a drug called captopril can protect the kidneys of diabetic patients from progressive, often fatal disease.

Third, the administration of the drug AZT to HIV-infected women during the last six months of pregnancy and to their newborn infants has cut the rate of transmission of this virus by two-thirds, without apparent ill effects. This method could save over 1,000 American children each year and many others worldwide from the ravages of HIV.

CONTRIBUTIONS OF BASIC SCIENCE

I emphasize these findings because they have obvious and important effects on human health and thereby fulfill the overarching goal of our agency. But each result, with its effects on prevention and treatment of disease, is the culmination of a much longer process that builds on many less-heralded discoveries in previous years, discoveries made possible by our Nation's traditional commitment to a long-term investment in basic biomedical science.

For example, the isolation of the colon cancer genes depended on over 30 years of developing techniques to localize genes on chromosomes and to grow them in bacteria. These techniques have also been used in the past year to isolate genes for Lou Gehrig's disease, Huntington's disease, and inherited cancers other than colon cancer.

Consider the development of captopril, the drug that benefits diabetic patients. That drug became available through the careful chemical study of an enzyme known as ACE. Inhibitors of ACE, like captopril, were first shown to control high blood pressure, another disease that damages the kidney. But the new role for the drug in diabetes is likely to be equally important.

Third, the prevention of maternal transmission of HIV through the use of AZT required both the chemical synthesis of AZT many years ago and the discovery that retroviruses from chickens and mice contain an unusual but essential enzyme, reverse transcriptase, that can be blocked by AZT. Both these events occurred long before we knew about either HIV or AIDS.

This look backwards makes a simple point. The clinical triumphs that we enjoy this year were possible only because we had invested successfully in many fields of basic science—bacteriology, virology, enzymology, chemistry and others. With the enlightened support of Congress, especially with the enthusiastic help of this committee and our great friend, William Natcher, NIH-funded scientists have continued to lead the world in virtually all fields of biomedical research, allowing forecasts of great benefit years or even many decades from now.

Consider just two recent developments. Investigators have learned how signals are transmitted to a cell and conveyed from the surface of the cell to the inner workings in the nucleus. These signals direct the cell's growth, differentiation, development, even its death. Understanding this network of signals heralds a revolution in the design of therapeutics for diseases like cancer that affect those basic cell processes.

Secondly, new techniques allow us to alter genes in the germ line of mice, permitting the creation of mice that carry mutations responsible for many of the most common human diseases. These genetically altered mice provide models for cystic fibrosis, for cancers, for metabolic and immunological disease like diabetes and lupus, with new prospects for understanding how disease arises and for testing new therapies.

As I mentioned at the outset, biomedical and behavioral scientists are exhilarated by such unprecedented opportunities, but we also feel constrained by economic factors that slow us down. Under such circumstances it is important to convince the public, you as representatives who provide our funds, and those scientists who compete to use them, that the NIH is making the best use of the money available.

Many of my efforts since assuming the directorship in late November have been directed to the goal of making the NIH more efficient and more fair. These efforts have been directed at both our intramural and extramural programs, and they concern personnel, peer review, management and policy.

Let me touch briefly on seven such initiatives.

INTRAMURAL PROGRAM REVIEW

First, the intramural program. As directed by you, the House Appropriations Subcommittee last year, I have conducted a careful review of the procedures that govern the intramural research program of NIH. A distinguished Subcommittee of the Advisory Committee to the Director has now made numerous recommendations in a draft document which has been provided to your subcommittee.

The report recommends more rigorous mechanisms for the recruitment, review and promotion of our scientists; improved methods for the training of our post-doctoral fellows and for recruitment of minority scientists, administrative measures that will help attract outstanding physicians and scientists to our program; procedures to allocate funds more fairly between intra-and-extramural programs; and, finally, a process for restructuring the Clinical Center Complex, beginning with a 250-bed hospital and linked research units. I welcome these recommendations and hope to put them into effect in the near future.

In the meantime, with my encouragement, the intramural program has already been strengthened by the formation of trans–Institute groups that focus on interdisciplinary issues like cell biology, genetics, and structural biology, as originally recommended by a committee of intramural scientists in 1992.

Second, in accord with recommendations that have been made in the past by committees evaluating the NIH directorship, many important authorities for promotions and appointments have been delegated to me by the Secretary of the Department of Health and Human Services and by the Assistant Secretary for Health. These new authorities will increase my ability to take decisive and timely action.

PEER REVIEW

Third is the issue of peer review. In the spirit of reinventing government, several initiatives are underway to improve the review of grant applications at NIH. The most significant of these is the use of triaging methods to allow study sections to focus upon those applications that are truly competitive. We are also examining the prospects for using computers to aid in the review of applications, procedures to avoid the unnecessary filing of forms, and procedures to improve the quality and range of expertise of study section members.

APPOINTMENT OF SCIENTIFIC OMBUDSMAN

Fourth, to ensure that the views of the extramural research community are well represented as we formulate policy at NIH, I have recruited an outstanding senior scientist, Dr. Howard Schachman of the University of California, Berkeley, to serve as an ombudsman. He travels frequently to major biomedical research institutions in which we have a major investment to listen to students, faculty, and administrators about their views. And I hope to appoint another such ombudsman who is more clearly responsible to the clinical research community in the near future.

BIOETHICAL ISSUES

Fifth, the success of biomedical science has required its leaders to confront new ethical and legal issues. I have devoted considerable attention to these questions in the past few months. The NIH has assembled, for example, panels to discuss human embryo research and the cosponsorship of research by government and industry. We have decided a few months ago that it is in the best interest of technology development to accept, without appeal, the patent office's rejection of NIH patent claims on human cDNA sequences. We have issued guidelines on clinical research that require incl sion of women and minorities. And we are assembling guidelin to advise grantee institutions on conflicts of interest.

DIVERSITY IN THE SCIENTIFIC COMMUNITY

Sixth, with respect to the diversification of the culture of science, as I indicated at my confirmation hearings in the Senate, I believe that the future health of our scientific enterprise requires the full development of the scientific talents of our entire society, including women, members of underrepresented minority groups, and those with disabilities. This will require closer attention to education and training at all levels. To these ends, we are implementing new programs, including loan repayment, to attract candidates from disadvantaged backgrounds to our training programs; centralizing our public and pre-college educational efforts in a single office; and developing a comprehensive program with the assistance of an EEO executive advisory group and the firm of Clifford Alexander and Associates to assure an equitable workplace for all NIH employees.

Finally, putting new plans into action in an institution as large as NIH requires a talented team. I have had the good fortune to attract outstanding people to important positions in my new administration. Many of these are sitting here at the table with me.

Among these are Dr. Ruth Kirschstein to my left, Deputy Director of NIH, well-known to this committee; Dr. Wendy Baldwin, further on my left, who is the Deputy Director for Extramural Research; Dr. William Paul, sitting down to my right, who is now the Director of the redesigned Office of AIDS Research; Dr. John Gallin, the Director of the Clinical Center; and Dr. Alan Leshner, the Director of the National Institute on Drug Abuse.

Searches are underway for a permanent Deputy Director for Intramural Research. The temporary Deputy Director is Dr. Michael Gottesman, sitting to my left. Searches are also underway for the Director of four other institutes, the Neurological Institute, and the Institutes for Dental Research, Mental Health, and Nursing Research. Finally, we are searching for a Director of the newly formed Office of Behavioral and Social Sciences.

THE FY 1995 BUDGET

Let me consider briefly the budget itself.

The President proposes to increase the NIH budget by $517 million above the fiscal year 1994 level to a grand total of $11.473 billion. This represents a 4.7 percent increase, slightly above the rate of inflation for biomedical research and substantially above the average ceiling imposed on discretionary spending by the Budget Reconciliation Act of 1993.

Given the constraints under which this budget was formulated, I believe it reflects the commitment of President Clinton and Secretary Shalala to basic science, technology, health care and an investment in the Nation's future.

The request for the coming year attempts to counter several specific threats to the health of the American people and to promote new initiatives that are likely to have wide benefits and sustain the vitality of fundamental research in biology, chemistry, behavioral science and other fields.

There are itemized increases in several areas of high priority: $78 million increase for the study of AIDS, with $10 million specifically targeted for topical microbicides to block transmission of infection; an $84 million increase for breast cancer, including $10 million for the Secretary's Breast Cancer Action Plan; and $5.8 million for tuberculosis.

We will spend more on neglected aspects of the health of women and minority populations, with increases of $5.6 million for the Office of Research on Women's Health, and a $10 million increase for the Minority Health Initiative.

Additional allocations of $24 million will be made for the application of high performance computing to science and medicine. Finally, substantial increases, over $300 million, will be devoted to the vast array of scientific activities that NIH traditionally supports, with only very slight variations in increments across the NIH Institutes, Centers, and Divisions.

With these funds, NIH expects to support 7,292 competing research project grants, or RPGs, for fiscal year 1995. Including support for noncompeting grants, NIH will fund a total of 23,890 RPGs. Overall, as shown on the chart that Ms. Little is displaying, the distribution of NIH resources differs only slightly from the distribution of funds 10 years ago, when the total budget was just under half of the current proposal. Both then and now, about 54 percent, the lion's share of the budget, is devoted to RPGs, with about 9 percent devoted to research centers, and 7 percent for research contracts.

The NIH intramural program received 11.6 percent in 1985 and will receive just under 11 percent in the current proposal. The relative cost of research management services is down slightly at 4.4 percent, and research training has fallen from 4.3 to 3.3 percent.

Mr. Chairman, it is my hope that this budget, combined with the seven broad initiatives I have described, will bring new ideas and new people into the service of NIH, will help us to embrace the magnificent new prospects for pursuing our traditional mandate, science in the service of human health.

I will be pleased to answer any questions you or your colleagues might have.

[The prepared statement and biography of Dr. Harold Varmus follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
Statement of the Director

Mr. Chairman, Committee Members:

I am pleased to appear before you for the first time as the Director of the National Institutes of Health to present the President's NIH budget for FY 1995. The President proposes to increase the NIH budget by $517 million above the current level, to $11.473 billion. This represents a 4.7% increment, slightly above the rate of inflation for biomedical research and substantially above the average ceiling imposed on discretionary spending by the Budget Reconciliation Act of 1993. Given the constraints under which this budget was formulated, I believe it reflects the commitment of President Clinton and Secretary Shalala to basic science, to technology, to health care, and to investment in the nation's future. The request for the coming year attempts to counter several specific threats to the health of the American people; to promote new initiatives that are likely to have wide benefits; and to sustain the vitality of fundamental research in biology, chemistry, behavioral science, and other fields. There are itemized increases for the study of AIDS, breast cancer, and tuberculosis; we will spend more on neglected aspects of the health of women and minority populations; additional allocations will be made for the application of high performance computing to science and medicine; and substantial increases (over $300 million) will be devoted to the vast array of scientific activities that NIH traditionally supports. We propose this budget with the recognition that the biological sciences are in a remarkable phase of growth, productivity, and promise. New methods based on physics, chemistry, and computer science are providing detailed visual images of the molecules that govern the behavior of cells, and these methods will usher in a new era in the development of drugs. Molecular biology has opened the window on our genetic endowment, and we are learning the composition and actions of genes that predispose us to disease when we inherit them in abnormal form. Biochemistry is teaching us how our cells respond to the environmental cues that govern growth and differentiation, providing new strategies for the diagnosis and treatment of cancer and other diseases. Neuroscience has revolutionized approaches to the normal brain, its individual cells, and the chemical signals that flow between them; to disorders of the nervous system; and to cognition and behavior. This is an era of expanding vistas, and the budget I am presenting today represents a compromise between fiscal necessities and scientific possibilities.

During the past year investigators supported by the NIH have reported many important achievements that illustrate the potential of NIH to improve the nation's health. A few examples suffice to display the significance of these advances.

(I) A gene that strongly influences the probability of developing a common form of colon cancer, diagnosed in over 10,000 Americans each year, has been isolated from human chromosome two. Approximately one million people in the U.S. have inherited an abnormal form of this gene and are thus at high risk of contracting the disease. It will soon be possible to identify these people by genetic screening methods; this will allow early detection of disease by colonoscopy and result in the saving of many lives.

(II) Two large-scale clinical studies have changed the standard for optimal management of diabetes. One has established unequivocally the value of precise control of blood sugar for preventing the major complications of insulin-dependent diabetes mellitus---blindness and kidney failure. The other has shown that the drug captopril can protect the kidneys of diabetic patients from progressive disease. In response to these findings, many of our nation's diabetics will have longer and healthier lives, and costs for management of complications will fall.

(III) The administration of AZT to HIV-infected women during the latter two thirds of pregnancy and to their new born infants has cut the rate of transmission of the virus by 75%, without apparent ill effects. Wide application of this method could save over 1,000 American children each year, and many others world-wide, from HIV-induced disease.

I emphasize these findings because they have obvious and important effects on human health, and thereby fulfill the overarching goal of our agency. But results of this sort, with their dramatic effects on prevention and treatment of disease, are the culmination of a process that builds on many, less-heralded discoveries in previous years---discoveries made possible by our nation's traditional commitment to a long-term investment in biomedical science.

Isolation of the colon cancer gene, for example, depended on over thirty years of developing techniques to localize genes on human chromosomes and to amplify them in bacteria. These techniques are, of course, being used to study many other genetic diseases, largely through the Human Genome Project. In just the past year, NIH-supported investigators have identified the genes for Lou Gehrig's Disease, Huntington's Disease, and inherited cancers other than colon cancer.

The function of the colon cancer gene was rapidly understood because the gene is closely related to bacterial and yeast genes that protect the integrity of DNA by repairing mutations in these other, much simpler organisms. In this way, over twenty years of support for basic studies of DNA damage and repair unexpectedly revealed a new and important mechanism for causing cancer, a mechanism that is likely to have a role in cancers arising in many other organs.

Development of captopril, the drug that benefits diabetic patients, became possible through the careful study of an enzyme, called ACE, that cleaves other proteins. One action of ACE is to convert a small protein to a smaller fragment that regulates blood pressure. Fundamental principles of chemistry were used in the 1970's and 1980's to design ACE inhibitors, such as captopril, that control hypertension, another disease that damages the kidney. The new role for the drug in diabetes is likely to be equally important.

The prevention of maternal transmission of HIV required at least two important events that preceded by many years any knowledge of AIDS or HIV:

(I) the chemical synthesis of AZT, which was originally tested as an anti-cancer drug in the 1960's, and (II) the discovery in 1970 that retroviruses from chickens and mice contain an essential enzyme, reverse transcriptase, with unusual properties, including susceptibility to inhibition by AZT.

This look backwards shows that the clinical triumphs that we enjoy this year have been possible only as a result of steady successes in many fields of basic science---especially bacteriology, virology, enzymology, chemistry, and molecular biology. Because of this relationship between fundamental discoveries in biology and later benefits to health, it is important to gauge the success of NIH in the past fiscal year not simply by the most recent clinical breakthroughs, but also by the standards of scientific productivity and excellence. By many commonly used criteria---publications, citations in the scientific literature, invited presentations at international meetings, prizes, patents, and applications for research training---the United States continues to lead the way in virtually all fields of biomedical research. Several areas of research were so extraordinarily productive in the past year that they need to be singled out, if only to anticipate the beneficial effects we can expect to flow from them in coming years.

(I) Through a combination of genetic and biochemical methods---often using simple experimental organisms, such as yeast, fruit flies, and worms, as well as cells in culture---investigators have learned how signals are transmitted through a cell to direct growth, division, differentiation, and even death. These signaling processes often begin at the surface of the cell and conclude in the nucleus, where genes are controlled. A profound understanding of cellular networks of communication heralds a revolution in the design of therapies for diseases that affect fundamental cell processes, such as cancer and developmental disorders.

(II) The burgeoning field of structural biology continues to provide us with extraordinary images of the three dimensional organization of proteins and nucleic acids. Among the most thrilling of this year's images was the picture of the major working unit of myosin, the piston in the cellular motor that allows muscles to work and subcellular elements to move. The achievement of this long-standing goal promises new approaches to the control of muscle diseases. For example, an inherited disease of heart muscle, responsible for many of the deaths of young athletes, has been traced to single changes at critical positions in myosin motors.

(III) Recently developed techniques to alter genes in the mouse germ line have been used to create mice carrying mutations responsible for many human diseases. These genetically-altered mice provide accessible models for cystic fibrosis, certain cancers, and metabolic and immunological diseases, such as diabetes and lupus. The new prospects for understanding how disease arises and for testing novel therapies are truly remarkable.

The picture I have drawn suggests that this is an especially challenging time to assume the leadership of the NIH. Biomedical and behavioral scientists are exhilarated by the unprecedented opportunities to understand biological systems and advance the healing arts, but we also feel constrained by the economic factors that slow our pursuit of those opportunities. Under such circumstances, it is important to convince the public that provides our funds, as well those scientists who compete to use them, that the NIH is making the best use of the money available.

Many of my efforts since assuming the directorship in late November have been directed to the goal of making the NIH more efficient and fair. These efforts have been directed at both our intramural and extramural programs, and they concern personnel, peer review, management, and policy.

(I) Improving the intramural research program. As directed by the Appropriations subcommittee last year, I have conducted a careful review of the procedures that govern the intramural research program. A distinguished subcommittee of the Advisory Committee to the Director has made numerous recommendations about our recruitment, evaluation, and promotion of NIH scientists; our training programs; our procedures for budget allocation and program planning; and our facilities, particularly the Clinical Center Complex. I welcome these recommendations and expect to put most of them into effect in the near future. (I will, of course, make the formal report of the subcommittee available to the Congress when it is completed.) In the meantime, with my encouragement, the intramural program has already been strengthened by the formation of inter-Institute groups that focus on cell biology, genetics, structural biology, neuroscience, and immunology, as originally recommended by a committee of intramural scientists in 1992.

(II) Installing new leadership. I have had the good fortune to attract outstanding people to important positions in my new Administration. Among these are Dr. Ruth Kirschstein, the Deputy Director of NIH; Dr. Wendy Baldwin, the Deputy Director for Extramural Research; Dr. William Paul, the Director of the redesigned Office of AIDS Research; Dr. John Gallin, the Director of the Clinical Center; and Dr. Alan Leshner, the Director of the NIDA. Searches are underway for a permanent Deputy Director for Intramural Research and Directors of four other Institutes (NINDS, NIDR, NIMH, and NINR) and of the newly formed Office of Behavioral and Social Sciences.

(III) Acquiring new authorities. In accord with recommendations that have been repeatedly made by committees evaluating the Office of the Director, NIH, many important authorities for promotions, appointments, and other matters have been delegated to me by the Secretary, HHS, and the Assistant Secretary for Health, HHS. These new authorities will increase my ability to take decisive and timely action on many issues.

(IV) Upgrading peer review. Several initiatives are underway to improve the procedures for review of grant applications at NIH. The most significant of these is the use of triaging methods to allow study sections to focus upon those applications that are truly competitive. Committees composed of NIH and extramural personnel are also examining the prospects for using computers to aid in the review of applications and looking for ways to improve the quality and range of expertise of study section members.

(V) Communicating with extramural scientists. To insure that the views of the extramural community are well represented in the formulation of NIH policy, I have recruited an outstanding senior scientist, Dr. Howard Schachman of UC Berkeley, to serve as an ombudsman for that community. Dr. Schachman travels frequently to major biomedical research institutions to listen to students, fellows, faculty at all levels, and administrators about their views on topics ranging from underfunded areas of research to peer review and scientific integrity.

(VI) Formulating policy. The successes of biomedical science have required its leaders to confront new ethical and legal issues. I have devoted considerable attention to these questions in the past few months. The NIH has assembled panels to discuss human embryo research and the co-sponsorship of research by government and industry; we have decided that it is not in the best interest of technology development to appeal a rejection of NIH patent claims on human cDNA sequences; and we are assembling guidelines to advise grantee institutions on conflicts of interest.

(VII) Enriching and diversifying the culture of science. As I indicated at my confirmation hearings before the Senate Committee on Labor and Human Relations, I believe that the future health of our enterprise requires full development of the scientific talents of our entire society---including women, members of under-represented minority groups, and those with disabilities. This will require closer attention to education and training at all levels. To these ends, we are creating new incentives, including loan repayment, to attract minority candidates to our training programs; centralizing our public and pre-college educational efforts in a single office; and developing a comprehensive program, with the assistance of Clifford Alexander and Associates, to assure a fair and equitable workplace for all NIH employees.

It is my hope that these initiatives will help the NIH to embrace the magnificent new prospects for pursuing our traditional mandate---science in the service of human health.

Thank you Mr. Chairman, I will be pleased to answer any questions you may have.

CURRICULUM VITAE

HAROLD ELIOT VARMUS, M.D.

Date of Birth: December 18, 1939
Place of Birth: Oceanside, New York

Education

Freeport High School, Freeport, New York		
Amherst College, Amherst, Massachusetts	B.A. magna cum laude	1961
Harvard University, Cambridge, Massachusetts	M.A.	1962
Columbia University, New York City, New York	M.D.	1966

Training

Intern in Medicine, Presbyterian Hospital, New York, 1966-1967.
Assistant Resident in Medicine, Presbyterian Hospital, New York City, 1967-1968.
Clinical Associate, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, 1968-1970.
Postdoctoral Fellow, Department of Microbiology, University of California Medical Center, San Francisco, California, 1970-1972.

Appointments

Lecturer, Department of Microbiology, University of California Medical Center, San Francisco, California, 1970-1972.
Assistant Professor in Residence, Department of Microbiology, University of California Medical Center, San Francisco, California, 1972-1974.
Associate Professor, Department of Microbiology, University of California Medical Center, San Francisco, California, 1974-1979.
Professor, Department of Microbiology and Immunology, University of California Medical Center, San Francisco, California, 1979 - Present, Department of Biochemistry and Biophysics, 1982 - Present.
American Cancer Society Professor of Molecular Virology, 1984 - Present.

Military Service

U.S. Public Health Service, Surgeon, 1968-1970.

Societies

Phi Beta Kappa (1961); Alpha Omega Alpha (1965); American Association for the Advancement of Science (1970); American Society for Cell Biology (1992), American Society for Microbiology (1971); American Society for Biochemistry and Molecular Biology (1984); American Society for Virology (1987); National Academy of Sciences (1984); American Academy of Arts and Sciences (1988); Institute of Medicine (1991).

Fellowships and Awards

Woodrow Wilson Fellow, 1961-1962
International Fellow of Columbia University, 1963-1964
Smith, Kline, and French Foreign Fellow (Bareilly, India), 1966
Senior Dernham Fellow, California Division, American Cancer Society, 1970-1972
USPHS Research Career Development Awardee, 1972-1977
Josiah Macy Scholar (Imperial Cancer Research Fund, London) 1978-1979
California Scientist of the Year, 1982
Albert Lasker Basic Medical Research Award, 1982
Passano Foundation Award, 1983
Armand Hammer Cancer Prize, 1984
Alfred P. Sloan Prize (General Motors Cancer Research Foundation) 1984
Simon M. Shubitz Cancer Prize, 1984
Gairdner Foundation International Award, 1984
D. Sc. (Hon.), Amherst College, 1984
Joseph Mather Smith Award, Columbia College of Physicians & Surgeons, 1986
American College of Physicians Award, 1987
Gold Medal, Alumni Association of the College of Physicians & Surgeons, 1989
Nobel Prize in Medicine or Physiology, 1989
D. Sc. (Hon.), Columbia University, 1990
University of California, San Francisco, Medal, 1990

Professional Activities

Editorial

Associate Editor, *Cell*, 1974-1978, 1979 - Present
Associate Editor, *Virology*, 1974 - 1984
Editor, *Molecular and Cellular Biology*, 1984 - 1988.
Associate Editor, *Genes and Development*, 1986 - Present
Editorial Board, *Trends in Genetics*, 1989 - Present
Editorial Board, *Proceedings of National Academy of Sciences*, 1987 - 1992
Editorial Board, *Cancer Surveys*, 1985 - Present
Editorial Board, *Current Biology*, 1992 - Present

Review Boards

Special Grants Committee, California Division of the American Cancer Society, 1973 - 1976
Breast Cancer Virus Working Group, Virus Cancer Program, National Cancer Institute, 1973 - 1974
Virology Study Section, National Institutes of Health, 1976 - 1980.
Personnel Committee, American Cancer Society, 1982 - 1986
Board of Scientific Counselors, Division of Cancer Biology and Diagnosis, National Cancer Institute, 1983 - 1987
Research Fellowship Committee, California Division, American Cancer Society 1986 - 1989
Searle Scholars Review Committee, 1988 - 1992
Genetics Scientific Review Board, Howard Hughes Medical Institute, 1990 - Present
Scientific Review Board, Sloan-Kettering Institute, 1991 - Present
Visiting Committee, Department of Cell and Developmental Biology, Harvard University, 1991 - Present

Industrial Consultation

Scientific Consultant, Chiron Corporation, 1982 - 1987
Scientific Advisory Board, Merck Corporation, 1985 - 1988
Scientific Advisory Board, Gilead Corporation, 1988 - Present
Chairman, Scientific Advisory Board, Onyx Corporation, 1992 - Present

Other

Chairman, Retrovirus Study Group, International Committee on Taxonomy of Viruses, 1981 - 1987
Chairman, Animal Cells and Viruses Gordon Conference, 1987
Human Gene Therapy Subcommittee, Recombinant DNA Advisory Committee, NIH, 1986 - 1989
Chairman, Board on Biology, National Research Council, 1991 - Present
Advisor, Congressional Caucus for Biomedical Research, 1990 - Present
Co-Chairman, New Delegation for Biomedical Research, 1991 - Present
Member, Joint Steering Committee for Public Policy of the Biomedical Societies, 1991 - Present

Intramural

Advisory Council, Medical Scientist Training Program, UCSF, 1977 - Present
Steering Committee, Department of Microbiology and Immunology, UCSF, 1982 - Present
Vice-Chairman, Board of Overseers, UCSF Biomolecular Resource Laboratory, 1986 - Present
Scientific Advisory Board, Gladstone Institute for Virology and Immunology (UCSF AIDS Research Center), 1992 - Present
Curriculum Committee, Department of Biochemistry and Biophysics
Chairman, Planning Committee for the UCSF Public Symposium on the DNA Revolution in Biology, 1992
Executive Committee, UCSF Transgenic Facility, 1991 - Present

PUBLICATIONS

Books

1. Varmus, H.E. and Levine, A.J. (eds.) Selected Readings in Tumor Virology. Cold Spring Harbor Laboratory, 1983.

2. Weiss, R., Teich, N., Varmus, H. and Coffin, J. eds. The Molecular Biology of RNA Tumor Viruses. 1982, 1984.

3. Stamatoyannopoulos, G., Neinhus, A.W., Majorus, P.W., Varmus, H.E., eds. The Molecular Basis of Blood Diseases. in press, 1993.

4. Varmus, H. and Weinberg, R. A. Genes and the Biology of Cancer. Scientific American Library, 1992.

LEGISLATIVE AUTHORITY

Mr. SMITH. Dr. Varmus, I want to ask you a couple of broad questions.

My memory goes back to Congressman Fogarty when he was chairman of this subcommittee, and then there was a Congressman from Indiana and then from Pennsylvania, and then I came on with Mr. Natcher in January, 1967.

During this period of time, we started out with a situation where there was really no earmarking by Institute at all. Especially when Fogarty was there, the Institutes were given so much money and you proceeded. Generally, that was the way it was.

Then we went through a period where the authorizing committee wanted to more specifically authorize by Institute. Generally speaking, these were limitations. I don't know of any new authority that was given by having these multiple authorizations. They have acted as limitations.

Then we went through a period where Dr. De Bakey and famous physicians would come before us and say we are about ready for a breakthrough. What we need is more money in this Institute—which meant less money somewhere else.

And so now we have gotten to where some people even want to authorize by disease. Maybe we will get down to where we have authorizations for mumps on the left side and mumps on the right side as separate authorizations and separate appropriations.

My question to you is a general one. How much damage or how much good are we doing by having these multiple authorizations broken down and broken down some more and broken down some more, rather than giving you broad authority to go ahead with basic research, which we don't know where it is going to lead to anyway?

Dr. VARMUS. Well, it is a complicated question, Mr. Smith, but let me begin by saying that in an ideal world you would trust us to make the allocation—the assignments of the funds you give us, and the citizenry would accept our ability to make the wisest of all reappropriations of the money within our Institutes and among our scientists.

We are not in an ideal world, and I think at this point the committee would like to know more about how we are going to spend the money than to simply give to NIH, as a whole, $11.5 billion. I think you have a right to know how we are going to subdivide that among our Institutes, how we are going to, in some general sense, appropriate that among the various diseases and basic science questions that we work on. And we are, of course, also responsive to our constituents, the public, who pay for this research and want a clearer sense of what we do with it.

Now there is a distinction between a designation of a large amount of money like a billion dollars to an institute that works on heart, lung and blood and a listing of specific objectives. The mission of each Institute covers a very large area including basic and clinical research. It is useful from the point of view of planning for each Institute to have some idea of what its specific budget is ahead of time.

It is also useful for us as an agency interested in persuading the public that their interests are very much our interests, to indicate to them that we spend a certain amount of money in the pursuit of a disease, AIDS, for example.

Now, we know that a vast amount of the money that we use to study AIDS is, of course, money being used to do the basic research required for making advances against that disease, basic research on viruses and the immune system and drug development and structural biology. So I see in some sense our subdivision of the budget into very large categories as a way of educating the public, and for that matter the Congress, to what we do and the way in which we use our money in the pursuit of certain health objectives that are clear to one and all.

Mr. SMITH. Well, are we breaking it down into too many pieces?

Dr. VARMUS. Well, I would argue that in the proposed budget this year this is not the case. I can imagine ways in which it could be broken down to directives as specific as funding a certain disease in a very specific way to do certain projects that are within our purview. That is an example of narrow earmarking, rather than providing support for a broad range of initiatives in an important area of science. There is a difference, in my mind, between those two directives.

SPENDING CAPS

Mr. SMITH. At one time, there was no limit on the amount of money that could be appropriated. But now we have a cap. For all practical purposes, we have got control, a cap.

And when we in this committee increase one Institute and, therefore, have to reduce another Institute, are we doing something that has a benefit or not?

Dr. VARMUS. Well, it is our hope that one can work within the spending caps and not decrease any Institute.

Mr. SMITH. I know, but as a practical matter we know there is a cap on how much money you can get. When we tinker around with increasing one thing because it happens to be popular at the time and that means reducing another, to start with, how much are we actually reducing research and increasing research in another area?

And in the second place, how much good and how much harm are we doing? Are you given the flexibility you need?

Dr. VARMUS. Well, there are two issues. One is flexibility and one is the funding level. And in the current budget, for example, with an overall 4.7 percent increase proposed for NIH, no Institute falls below a 3.5 or 3.6 percent increase, without investments.

Now, whenever we fall below the inflationary rate——

Mr. SMITH. Do you know at this point precisely how much increase you need in each Institute or will you not know that until sometime during the fiscal year of 1995?

Dr. VARMUS. Well, the issue of need is a tough one to define, and we have to balance what we see as scientific opportunity, which I would say——

Mr. SMITH. You don't know at this point where the opportunities are going to be?

SCIENTIFIC OPPORTUNITIES

Dr. VARMUS. I would say scientific opportunity is considerable in advance of what we are able to propose, because of the caps on discretionary spending.

We do have some flexibility in the budget for two reasons. One, we do have one percent transfer authority that allows me to move money from one Institute to another during the year. And, secondly, I have a discretionary fund—or have had in the past. We are asking for one again this year. This fund gives me the ability to make responses to emergent needs or new opportunities to make advances. And I have planned to use the money that way.

Mr. SMITH. Well, you anticipated the question I was leading up to. Is the one percent enough? Is the flexibility enough to take advantage of new opportunities that you don't know of?

Dr. VARMUS. The one percent transfer authority is for emergency use only, but it is a substantial amount of money considering that our total budget is going to be over $11 billion. At least we hope it will be.

ALLOCATING FUNDS BY DISEASE AREA

Mr. SMITH. Well, as you might detect, I am really concerned about the tendency of Members of Congress, Members of the House and Senate both, to want to identify funding by disease and to want to put out a press release: I got X number of dollars increase for this disease or that disease. And we are talking about basic research.

Dr. VARMUS. We are, for the most part. About 60 percent of our budget would be designated as basic research, but a large fraction of that can also be described as being in the pursuit of some large collection of diseases.

For example, we do a great deal of research on the basic properties of nerve cells. It would be called basic neuroscience. We can list a class of diseases of the nervous system that are very likely to profit from our deeper understanding of how nerve cells work.

INDIRECT COSTS

Mr. SMITH. The other question has to do with the cost for overhead. We didn't pay much attention to that. As a matter of fact, we gave Dr. Shannon more money than he could possibly get rid of, in the early years. And so they increased overhead any way they could to try to get rid of the money.

We are at the point now where any increase in overhead reduces the amount of money that is available to some team out there that is not going to be funded.

Dr. VARMUS. Well, the government is committed to paying the full cost of research, and the cost of research at universities does involve the kinds of activities that are supported by indirect cost reimbursements. I came from the extramural community and I am well aware of what is supplied to investigators at universities and private institutions in the way of services that need to be paid for if the government is going to assume the responsibility of paying for research.

Mr. SMITH. Well, when indirect costs are double at one university compared to what they are at another, can we justify not considering then which university gets the research grant? Because we are only going to get half as much research from one university as we do from another.

Dr. VARMUS. I think it is difficult. I would be cautious about assuming that a higher indirect cost rate would mean that there will be a lower return on the research. I think one has to look at the history of the institution, how it supports its scientists, the nature of the research activity that goes on there.

Efforts in the past to try to normalize indirect cost rates in biomedical research have run into difficulty because of the need to appreciate the historical development and the nature of research activities at different universities.

A great deal of attention has been paid in the last few years by the OMB, by the Department, by Congress, by biomedical research investigators and by administrators to the redesign of indirect cost regulations. The result of that activity was the reissuance of Circular A–21 last year, which does place caps on administrative spending and tries to offer incentives for reduction of administrative expenses and indirect costs by offering a threshold rate that removes an obligation to negotiate the rate. But it is more difficult to control other aspects of indirect cost reimbursements by a draconian uniform rate.

Mr. SMITH. Well, the rates did run all the way from 40 percent to 90 percent and over 90 percent. Under the new rules that you have, what is going to be the variance?

Dr. VARMUS. Well, the cap is on administrative costs, and this cap is 26 percent. But there is considerable variation in the other categories. The highest rate is something on the order of 70 percent on the latest list I have just been provided.

Mr. SMITH. And what is the lowest?

Dr. VARMUS. The lowest rates are often at universities that have a component of State support. The numbers are as low as 37 percent.

Mr. SMITH. Thirty-seven to 80 instead of 40 to 92. It is a little progress, I guess, but it is sure a big variance.

Dr. VARMUS. There have been clear indications that, on the whole, indirect cost rates are coming down.

Mr. SMITH. The attention to it is helpful.

Dr. VARMUS. It has helped. There is no doubt about that.

One of the things we are trying to do in our efforts to streamline peer review is to remove some of the obligations to file paperwork on the over 70 percent of grants that will never get funded. That may represent a significant administrative cost savings that will further help reduce indirect cost rates.

Mr. SMITH. I think the universities ought to know that they are going to continue to be watched. We don't want any more of this publicity.

Dr. VARMUS. I am sure some of your colleagues have made them aware they are being watched.

Mr. **Smith**. You know, it is just ridiculous what they were putting into indirect costs. Because it comes right directly out of the amount of research that we are going to get that we need. And we have got more opportunities to make grants than we are going to be able to fund.

[The information follows:]

INDIRECT COST RATES OF MAJOR COLLEGES AND UNIVERSITIES

Major Colleges and Universities
FY94 On-Campus Organized Research Rates By Grouping

Facilities = O&M and Depreciation/Use Allowance
ADMGP = G&A, DA and SPA
Other = Student Services,C/F Adjustment and Miscellaneous

Yr	#	Name of Institution	Facilities	ADMGP	Library	Other	IDCR
94	1	ALBANY MED COLLEGE	25.60%	26.00%	2.80%	0.00%	54.40%
94	2	ARIZONA STATE UNIV.	23.50%	26.00%	1.40%	0.10%	51.00%
94	3	BAYLOR COLLEGE OF MEDICINE	21.00%	26.00%	0.50%	0.00%	47.50%
94	4	BOSTON UNIV.	30.16%	26.00%	2.00%	3.84%	62.00%
94	5	BOWMAN GRAY SCHOOL OF MEDICINE	18.00%	25.00%	2.00%	0.00%	45.00%
94	6	BRANDEIS UNIV.	21.10%	26.00%	2.30%	0.00%	49.40%
94	7	Brown University	29.95%	23.90%	1.26%	0.89%	56.00%
94	8	California Institute of Technology	34.35%	15.91%	3.18%	3.08%	56.72%
94	9	Carnegie-Mellon University	31.20%	26.00%	2.42%	4.20%	63.82%
94	10	CASE WESTERN RESERVE	24.80%	24.70%	1.50%	0.00%	51.00%
94	11	COLORADO STATE UNIV.	17.10%	26.00%	1.10%	0.50%	44.70%
94	12	Columbia University	32.19%	25.99%	5.02%	3.80%	67.00%
94	13	Cornell University(Endowed)	35.32%	26.00%	7.13%	-1.45%	67.00%
94	14	Cornell University(Medical)	34.79%	26.00%	2.69%	6.72%	70.20%
94	15	DARTMOUTH COLLEGE	30.40%	26.00%	3.60%	2.00%	62.00%
94	16	DUKE UNIV.	22.40%	26.00%	2.40%	0.00%	50.80%
94	17	EMORY UNIV.	32.00%	23.30%	1.70%	0.00%	57.00%
94	18	FLORIDA STATE UNIV.	20.90%	26.00%	1.10%	0.00%	48.00%
94	19	GEORGE WASHINGTON UNIV.	19.80%	26.00%	4.00%	0.00%	49.80%
94	20	GEORGETOWN UNIV.	32.50%	26.00%	2.50%	0.00%	61.00%
94	21	Georgia Institute of Technology	17.20%	26.00%	0.90%	-7.10%	37.00%
94	22	HARVARD MED SCH	75.80%	26.00%	2.00%	-20.80%	83.00%
94	23	HARVARD UNIV.	30.36%	23.60%	5.70%	9.84%	69.50%
94	24	HOWARD UNIV.	35.00%	26.00%	2.00%	0.00%	63.00%
94	25	INDIANA UNIVERSITY	24.70%	26.00%	2.00%	0.00%	52.70%
94	26	IOWA STATE UNIVERSITY	20.90%	22.90%	0.20%	0.00%	44.00%
94	27	JOHNS HOPKINS UNIV.	39.50%	25.00%	2.00%	0.00%	66.50%
94	28	LEHIGH UNIV.	29.60%	26.00%	3.40%	0.00%	59.00%
94	29	LOUISIANA STATE UNIVERSITY	21.00%	23.00%	1.00%	0.00%	45.00%
94	30	LOUISIANA STATE UNIV. MEDICAL CENTER	15.70%	25.30%	1.00%	0.00%	42.00%
94	31	Massachusetts Institute of Technology	37.47%	18.47%	2.59%	3.47%	62.00%
94	32	MEDICAL COLLEGE OF WISCONSIN	25.90%	22.50%	1.60%	0.00%	50.00%
94	33	MEDICAL UNIV. OF SOUTH CAROLINA	17.10%	26.00%	0.90%	0.00%	44.00%
94	34	MICHIGAN STATE UNIVERSITY	19.48%	24.52%	1.00%	0.00%	45.00%
94	35	MOUNT SINAI SCHOOL OF MED	34.88%	26.00%	1.18%	1.44%	63.50%
94	36	New Mexico State University	12.50%	26.00%	0.40%	-0.80%	38.10%
94	37	NEW YORK UNIV.	27.27%	26.00%	1.73%	0.00%	55.00%
94	38	NEW YORK UNIV. MED CENTER	27.16%	26.00%	2.93%	1.11%	57.20%
94	39	NORTH CAROLINA STATE UNIV. @ RALEIGH	19.10%	26.00%	1.90%	0.00%	47.00%
94	40	NORTHWESTERN UNIVERSITY	24.00%	26.00%	3.70%	0.00%	53.70%
94	41	OHIO STATE UNIVERSITY	18.53%	26.00%	1.47%	0.00%	46.00%
94	42	OKLAHOMA STATE UNIVERSITY	20.20%	22.90%	1.90%	0.00%	45.00%
94	43	OREGON STATE UNIV.	13.30%	26.60%	1.80%	0.30%	60.00%
94	44	Pennsylvania State University	22.67%	20.57%	0.74%	0.91%	44.89%
94	45	Princeton University	20.96%	26.00%	12.04%	0.00%	59.00%
94	46	PURDUE UNIVERSITY	25.00%	25.00%	1.00%	0.00%	51.00%
94	47	RENSSELAER POLYTECH INST.	28.30%	24.80%	1.90%	0.00%	55.00%
94	48	RICE UNIVERSITY	19.50%	26.00%	3.50%	0.00%	49.00%
94	49	ROCKEFELLER UNIV.	25.00%	26.00%	4.40%	5.60%	61.00%
94	50	RUTGERS UNIV.	29.16%	26.00%	1.84%	2.00%	59.00%
94	51	Stanford University	28.06%	26.00%	5.59%	1.35%	61.00%
94	52	ST.LOUIS UNIVERSITY	23.60%	18.80%	2.60%	0.00%	45.00%
94	53	SUNY HEALTH SCIENCE CNTR AT BKLYN-DOWNST	21.98%	26.00%	1.32%	0.00%	49.30%
94	54	SUNY @ ALBANY	19.83%	26.00%	1.37%	0.00%	47.20%
94	55	SUNY @ BUFFALO	24.02%	26.00%	1.48%	0.00%	51.50%
94	56	SUNY @ STONY BROOK	20.19%	26.00%	1.91%	0.00%	48.10%
94	57	Syracuse University	24.63%	26.00%	2.69%	0.58%	53.90%
94	58	TEMPLE UNIV.	26.80%	26.00%	1.00%	0.20%	54.00%
94	59	TEXAS A&M UNIVERSITY	21.10%	23.00%	0.90%	0.00%	45.00%
94	60	TEXAS TECH UNIVERSITY	21.00%	22.50%	0.50%	0.00%	44.00%

Major Colleges and Universities
FY94 On-Campus Organized Research Rates By Grouping

Facilities = O&M and Depreciation/Use Allowance
ADMGP = G&A, DA and SPA
Other = Student Services,C/F Adjustment and Miscellaneous

Yr	#	Name of Institution	Facilities	ADMGP	Library	Other	IDCR
94	61	THOMAS JEFFERSON UNIV.	40.30%	24.00%	1.20%	0.00%	65.50%
94	62	TUFTS UNIV.	36.96%	26.00%	1.04%	0.00%	64.00%
94	63	TULANE UNIVERSITY MED. SCHOOL	22.50%	26.00%	1.50%	0.00%	50.00%
94	64	UNIV. OF ALABAMA @ BIRMINGHAM	17.10%	24.70%	0.70%	0.00%	42.50%
94	65	Univ. of Alaska	17.00%	26.00%	1.30%	1.70%	46.00%
94	66	UNIV. OF ARIZONA	24.50%	24.20%	2.00%	0.80%	51.50%
94	67	UNIV. OF CALIFORNIA @ BERKELEY	21.90%	26.00%	1.50%	0.10%	49.50%
94	68	UNIV. OF CALIFORNIA @ DAVIS	16.10%	24.30%	2.50%	1.10%	44.00%
94	69	UNIV. OF CALIFORNIA @ IRVINE	22.20%	25.00%	2.00%	0.30%	49.50%
94	70	UNIV. OF CALIFORNIA @ LOS ANGELES	24.50%	22.50%	1.50%	0.50%	49.00%
94	71	UNIV. OF CALIFORNIA @ RIVERSIDE	17.70%	25.00%	1.90%	0.40%	45.00%
94	72	UNIV. OF CALIFORNIA @ SAN DIEGO	19.20%	26.00%	3.00%	2.30%	50.50%
94	73	UNIV. OF CALIFORNIA @ SAN FRANCISCO	15.50%	25.50%	1.70%	0.30%	43.00%
94	74	UNIV. OF CALIFORNIA @ SANTA BARBARA	17.50%	26.00%	1.20%	0.30%	45.00%
94	75	UNIV. OF CHICAGO	29.00%	23.70%	2.30%	0.00%	55.00%
94	76	UNIV. OF CINCINNATI	25.10%	26.00%	1.80%	0.00%	52.90%
94	77	UNIV. OF COLORADO	14.30%	26.00%	3.20%	0.00%	43.50%
94	78	UNIV. OF COLORADO HSC	23.50%	26.00%	2.00%	0.00%	51.50%
94	79	UNIV. OF CONNECTICUT	20.40%	26.00%	2.60%	-1.60%	47.40%
94	80	UNIV. OF CONNECTICUT HSC	20.30%	26.00%	1.70%	0.00%	48.00%
94	81	Univ. of Dayton	21.73%	21.79%	1.37%	0.42%	45.31%
94	82	UNIV. OF DELAWARE	27.80%	26.00%	2.00%	0.00%	55.80%
94	83	UNIV. OF FLORIDA	22.60%	20.70%	1.70%	0.00%	45.00%
94	84	UNIV. OF GEORGIA	18.40%	26.00%	1.30%	0.00%	45.70%
94	85	Univ. of Hawaii @ Manoa	21.13%	24.14%	2.45%	-2.72%	45.00%
94	86	UNIV. OF HOUSTON	22.60%	24.00%	1.90%	0.00%	48.50%
94	87	Univ. of Illinois @ Chicago	20.08%	26.00%	1.72%	0.00%	47.80%
94	88	Univ. of Illinois @ Urbana	24.90%	26.00%	2.70%	0.00%	53.60%
94	89	UNIV. OF IOWA	21.50%	21.70%	1.80%	0.00%	45.00%
94	90	UNIV. OF KANSAS	17.00%	26.00%	1.00%	0.00%	44.00%
94	91	UNIV. OF KANSAS MEDICAL CENTER	22.00%	25.50%	1.50%	0.00%	49.00%
94	92	UNIV. OF KENTUCKY	21.40%	26.00%	0.50%	0.10%	48.00%
94	93	UNIV. OF MARYLAND @ BALTIMORE	21.81%	26.00%	1.84%	0.00%	49.65%
94	94	UNIV. OF MARYLAND @ COLLEGE PARK	20.00%	26.00%	2.00%	0.00%	48.00%
94	95	UNIV. OF MASS. MED SCH @ WORCESTER	24.80%	26.00%	2.70%	3.50%	57.00%
94	96	UNIV. OF MASS. @ AMHERST	23.51%	26.00%	2.49%	0.00%	52.00%
94	97	UNIV. OF MED AND DENT OF NEW JERSEY	31.00%	26.00%	2.00%	0.00%	59.00%
94	98	UNIV. OF MIAMI-MED SCHOOL	26.30%	26.00%	1.50%	0.00%	53.80%
94	99	UNIV. OF MICHIGAN	24.00%	26.00%	2.00%	0.00%	52.00%
94	100	UNIV. OF MINNESOTA	17.70%	21.10%	1.20%	0.00%	40.00%
94	101	UNIV. OF MISSISSIPPI	17.00%	26.00%	1.00%	0.00%	44.00%
94	102	UNIV. OF MISSOURI @ COLUMBIA	21.00%	23.00%	1.00%	0.00%	45.00%
94	103	UNIV. OF NEW HAMPSHIRE	17.79%	26.00%	0.31%	0.00%	44.10%
94	104	UNIV. OF NEW MEXICO-MED. SCHOOL	21.60%	26.00%	0.90%	0.00%	48.50%
94	105	UNIV. OF NORTH CAROLINA @ CHAPEL HILL	16.50%	26.00%	2.00%	0.00%	44.50%
94	106	UNIV. OF NORTH DAKOTA	14.70%	24.60%	2.00%	0.00%	41.30%
94	107	Univ. of Notre Dame	18.50%	23.30%	2.90%	0.00%	44.70%
94	108	UNIV. OF OKLAHOMA	19.80%	26.00%	1.70%	0.00%	47.50%
94	109	UNIV. OF OREGON	21.40%	26.00%	2.10%	0.50%	50.00%
94	110	UNIV. OF OREGON HSC	18.80%	26.00%	1.20%	0.00%	46.00%
94	111	UNIV. OF PENNSYLVANIA	34.40%	25.10%	2.80%	0.20%	62.50%
94	112	UNIV. OF PITTSBURGH	21.50%	26.00%	1.50%	0.00%	49.00%
94	113	Univ. of Rhode Island	15.39%	27.94%	0.61%	-7.64%	36.30%
94	114	Univ. of Rochester	28.07%	25.91%	3.02%	0.00%	57.00%
94	115	UNIV. OF SOUTH CAROLINA	17.30%	26.00%	1.10%	1.60%	46.00%
94	116	UNIV. OF SOUTHERN CALIFORNIA	34.80%	25.90%	2.10%	0.20%	63.00%
94	117	UNIV. OF TENNESSE @ KNOXVILLE	16.00%	23.00%	2.00%	0.00%	41.00%
94	118	UNIV. OF TENNESSEE CTR FOR HLTH SCIENCES	18.90%	22.80%	0.80%	0.00%	42.50%
94	119	UNIV. OF TEXAS CANCER CENTER	23.81%	23.67%	0.52%	0.00%	48.00%
94	120	UNIV. OF TEXAS HSC @ HOUSTON	25.00%	23.00%	1.00%	0.00%	49.00%

Major Colleges and Universities
FY94 On-Campus Organized Research Rates By Grouping

Facilities = O&M and Depreciation/Use Allowance
ADMGP = G&A, DA and SPA
Other = Student Services,C/F Adjustment and Miscellaneous

Yr	#	Name of Institution	Facilities	ADMGP	Library	Other	IDCR
94	121	UNIV. OF TEXAS HSC @ SAN ANTONIO	23.00%	19.50%	1.00%	1.50%	45.00%
94	122	UNIV. OF TEXAS MED. BR. @ GALVESTON	27.00%	19.30%	3.20%	0.00%	49.50%
94	123	UNIV. OF TEXAS SOUTHWESTERN MEDICAL CENT	25.20%	21.80%	1.50%	0.00%	48.50%
94	124	UNIV. OF TEXAS @ AUSTIN	27.32%	20.90%	0.78%	0.00%	49.00%
94	125	UNIV. OF UTAH	24.30%	24.00%	1.20%	0.00%	49.50%
94	126	UNIV. OF VERMONT & STATE AG. COLLEGE	22.80%	25.00%	2.20%	0.00%	50.00%
94	127	UNIV. OF VIRGINIA	25.50%	23.50%	3.00%	0.00%	52.00%
94	128	UNIV. OF WASHINGTON	21.50%	26.00%	2.10%	0.40%	50.00%
94	129	UNIV. OF WISCONSIN @ MADISON	17.14%	25.00%	1.86%	0.00%	44.00%
94	130	UNIV. OF WYOMING	17.20%	23.00%	0.80%	0.00%	41.00%
94	131	UTAH STATE UNIV.	14.50%	21.50%	1.00%	0.00%	37.00%
94	132	VANDERBILT UNIV.	27.60%	26.00%	2.10%	0.30%	56.00%
94	133	VIRGINIA COMMONWEALTH UNIV.	16.40%	26.00%	2.60%	0.00%	45.00%
94	134	VIRGINIA POLY. INST. AND STATE UNIV.	25.20%	25.80%	2.50%	0.00%	53.50%
94	135	WASHINGTON STATE UNIV.	17.47%	26.00%	1.53%	0.00%	45.00%
94	136	WASHINGTON UNIVERSITY	32.50%	19.50%	1.90%	0.10%	54.00%
94	137	WAYNE STATE UNIVERSITY	24.54%	24.96%	1.50%	0.00%	51.00%
94	138	YALE UNIV.	35.00%	26.00%	3.00%	0.00%	64.00%
94	139	YESHIVA UNIV.	37.90%	26.00%	2.00%	0.00%	65.90%

118 = HHS Cognizant (per Blue Book 93 version)
20 = Major Schools DOD (ONR Cognizant)
1 = Princeton University (Dept of Energy)

Mr. SMITH. Mr. Porter.

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Varmus, all of us are just delighted that you have come to NIH. We welcome you. We commend you for the team of scientists and administrators that you have assembled and are assembling, and we knew you had excellent judgment when you chose Dr. Kirschstein to be your Deputy Director.

Dr. VARMUS. Thank you.

ANNUAL GROWTH IN NIH FUNDING

Mr. PORTER. Now, can I give you a very quick piece of advice? If the Chairman says to you, "Do you have enough flexibility in the NIH budget," just say no. And if he says "Do you want less interference from Congress in detailing what you can do," just say yes, less interference. He gave you a big opening there. You have got to drive the truck right through it.

All of us on this subcommittee are great believers in biomedical research. Research creates and sustains high-skill, high-paying jobs in America. It supports the world's leading biomedical research enterprise in the United States, which makes this country competitive and generates a positive balance of trade. And NIH is critical to maintaining our leadership in this important industry and is necessary to support the development of the biotech industry, which is one of the fastest growing in the country and grew directly out of NIH research.

Most importantly, through prevention, early diagnosis and early treatment, research holds the key to broadening access to health care services for all Americans, while containing costs.

Now, following up on what the Chairman said a few minutes ago, last week I asked Secretary Shalala to do something that I often ask Institute Directors to do: Forget about funding constraints and tell us what she thought was a reasonable level of long-term annual growth for NIH.

Now the Secretary indicated that the Biomedical Research and Development Price Index was the absolute minimum. For 1995, that index is estimated to be 4.1 percent.

But I would note that once the delayed obligations are removed from the President's budget—and we don't like delayed obligations for anyone, particularly for NIH—the President's budget actually comes in at less than 4.1 percent.

And if you further control for AIDS and breast cancer earmarks, the nontargeted research comes in at far below 4.1 percent. So could you answer this question, please? Forget about the budget constraints, and in your professional opinion tell us what you feel is a desirable growth rate for NIH in the long term.

Dr. VARMUS. As a watermark, Mr. Porter, I would begin by saying that we should be aiming to fund something in the order of 35 to 40 percent of our research applications. This would immediately increase our budget by about 30 percent.

Secondly, I think there are other areas of research and training that would benefit from increments in our budget. This applies particularly to the areas of training where we need to increase stipends for both graduate and post-doctoral salaries, to infrastructure, to instrumentation grants, and to a number of areas where we have been underfunding a research activity and allowed research facilities to deteriorate beyond the levels at which they can efficiently operate.

There are a number of special initiatives in the area of genetics and neuroscience that I would like to see advanced by a special initiatives as well. I would like to see us be able to afford more clinical research. There are many things that we could do in a more directed way, very expensive projects that are currently unavailable because of the shortage of funds.

So, overall, I would imagine an increase of about 40 percent in our funding.

ADMINISTRATION OF AIDS FUNDING

Mr. PORTER. The 30 percent that you originally mentioned would translate into, if my arithmetic is correct, something around 6 percent at an annual rate of increase, which I personally believe is a minimum for NIH and what this subcommittee was able to put into its mark in fiscal 1994.

Let me ask about AIDS for a second. Last year, the NIH Revitalization Act authorized a new system for funding AIDS research. To implement that Act the administration is proposing a consolidated AIDS line item. Did the Department consider other alternatives to the consolidated line item, and are those alternatives consistent with the statute?

Dr. VARMUS. We did consider other ways to manage AIDS funding, but the only one that seems to me to accurately represent the spirit of the new legislation is to appropriate the money directly to the Office of AIDS Research. That office would, then, distribute the monies promptly to the Institutes in compliance with the provisions of the AIDS comprehensive plan.

Mr. PORTER. Well, I understand the need to strengthen the AIDS research planning process across all of the Institutes. However, I am not convinced that a consolidated line item is the best way to do it. I am concerned that the administration's proposal vests too much authority in one individual who is neither the NIH Director nor an Institute Director. And I am not speaking of that particular individual, I am talking about the office. The individual I have great confidence in.

Secondly, I think this sets a very bad political precedent. If we do this for AIDS, why shouldn't we do it for every other disease?

Third, by appropriating to the AIDS office, we break the traditional approach to appropriating by Institute and we cede the committee's authority and responsibility for allocating funds among the Institutes.

Dr. Varmus, when we talked last week—I know that you support the budget request, you said, this morning, but before you came to NIH you had your reservations about this approach to budgeting for AIDS. I would appreciate your telling the committee why you objected to the NIH Revitalization Act before coming to NIH.

Dr. VARMUS. I don't think it serves a tremendous amount of purpose to go back over the history of my reluctance to support a bill which was still then in its very early stages and doesn't represent the bill as it now stands. But I would like to address some of the concerns you brought up about how the AIDS budget is formulated.

First of all, that budget is not in the hands solely of Bill Paul, competent as he is. We don't entrust him with that complete responsibility. The budget is formulated by a series of coordinating committees, five in number, that were first put into place by Tony Fauci, the previous Director of that Office. Those five committees represent the major disciplines in AIDS, and they are constituted by members of all the Institutes that have major investments in those areas of AIDS research. So the budget is very much a consensus process, maybe more so than the formation of any other budget line in our budget.

Secondly, there are, of course, other Institutes, the National Cancer Institute to name just one, that have budgets that are organized around the goal of studying a disease, just as the Office of AIDS Research does.

So I think that the way in which the budget is currently being put together does meet many of the principles that I think you and I would adhere to.

INCREASED SUPPORT FOR AIDS RESEARCH

Mr. PORTER. The administration has gone to great pains to break out AIDS in its budget submission and, while I would prefer not to have this discussion, I believe the President may have crossed the line between strategic planning and earmarking, which I know that you opposed in the Senate hearing. AIDS is the number nine killer, yet we make a greater investment per case of AIDS, per death and per year of potential life lost, than for any other disorder or disease.

In 1994, the administration is increasing AIDS research funding by 21 percent. Yet, for 1995, the administration is proposing an increase of 6 percent for AIDS research compared to 4.7 percent for NIH overall. These figures seem to indicate to me that NIH is overinvesting, perhaps, in AIDS relative to the impact of the syndrome and given our funding constraints.

For instance, heart disease is the number one killer and disproportionately affects minorities. Yet we spend $1,020 per heart disease death compared to $22,820 per AIDS death. Even controlling for years of potential life lost, the disparity remains. How does NIH justify these priorities, a much greater increase in AIDS research than for non-AIDS research?

Dr. VARMUS. Well, of course this year it is not a much greater increase for AIDS research. But I think it is a mistake to try to analyze the budget by determining the number of dollars spent per disease-related death. We have to spend our money in accordance both with medical urgency and with scientific opportunity.

AIDS is an infectious disease. It is a disease we ought to be able to stop with respect to transmission. It is a disease caused by a virus we hope very much to be able to defeat. It is a disease that attacks young people in particular. It also, of course, has a disproportionate effect on minority populations.

There are many enormous scientific opportunities that we see for understanding how this virus works and developing new drugs and vaccines that might have a very powerful effect upon a disease that threatens a very large segment of our population and, indeed, the entire world. We have a responsibility as the leading country in the world in biomedical research to worry about this disease which is spreading rampantly throughout many parts of the world in addition to the United States and Europe.

EFFECT OF AIDS RESEARCH ON OTHER DISEASES

Mr. PORTER. I will agree with that, but I could make the same case for heart disease, cancer or diabetes or many others.

Dr. VARMUS. We do have major investments, as you know, in all those areas. In fact, investment in cancer is somewhat larger. But we do have to form our budget in accordance with the kinds of experiments, and the number of investigators in the field who are working on these problems. It is difficult to apportion the budget as a fraction of fatalities from the disease in question.

Now, I should point out that the money that is being used to study the AIDS virus and the immune system is generating results that are not simply pertinent to AIDS. The results that have come out of our intensive study of this virus and the immune system that the virus attacks are relevant to many other diseases—many important diseases. The intensity of research in this area is having a rippling effect in many other areas of research that are important in autoimmune disorders, other infectious diseases, the design of vaccines, and an understanding of basic mechanisms of cell function.

So I think that we are dealing with a very intensive research arena in which investment of money has been shown to pay off.

PERSONNEL CONSTRAINTS

Mr. PORTER. Let me finally ask in this round—this is a softball—the NIH is under tight funding and personnel constraints given the 1995 budget. What is the biggest problem the biomedical research enterprise faces and what is your biggest challenge as chief administrator of NIH?

Dr. VARMUS. Those are two separate problems. I think the biggest problem we face as the caretaker of biomedical research in this country is inadequate funding, that we have investigators in the extramural community who are suffering from low success rates in grant applications, that we are giving a poor signal to people who would like to enter the field of biomedical research, arguably the most exciting intellectual activity of this part of our century, However, they see their senior mentors suffering under the difficulties of obtaining adequate grant support.

With respect to my role as an administrator, I see at least two or three major problems facing us at NIH. The first is the difficulty of adapting to the governmental directives to reduce our FTEs, particularly at the higher levels of our employment scale. These folks at NIH are not middle-level managers. They are scientists running laboratories. This poses a severe problem for us.

The second problem I am facing as administrator is establishing an equitable workplace at NIH and making sure that NIH functions in a way that is fair to all and encourages women, minorities, and people with disabilities. We are struggling hard with these problems.

Mr. PORTER. It is kind of a great irony that with the end of the Cold War everyone expected we would have more resources available to do the things that are important and that we would be able to get rather large increases—at least that was my thinking five or six years ago—get large increases for NIH that would really be able to move us forward very rapidly. And here we are at the end of the Cold War, and we have exhausted our own resources in bringing it about, and here we are under very tight constraints.

That means it is up to us to look at the priorities and decide which ones are most important within our jurisdiction and to fund those that are. In my opinion, you have the most important priority, and we want to do the best we possibly can to support that.

Dr. VARMUS. I appreciate your sentiments.

Mr. SMITH. Four new Members have shown up. We will stay as long as we need to so everybody can ask all the questions they want to, but on the first round let's try to stay within 10 minutes.

Mr. Stokes.

ESTABLISHING AN EQUITABLE WORKPLACE AT NIH

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Varmus, let me welcome you and your associates here this morning. It is a pleasure to welcome you before our subcommittee.

I also want to express my appreciation for the fact that you have made yourself available to discuss many of the issues regarding your budget even before your appearance here. Some of the matters that I will discuss with you here, you and I have discussed in private earlier. However, it is important that these matters be placed on the record.

I want to take a moment, also, to commend you for the very strong statement you made both in your formal presentation and in your additional comments this morning regarding your commitment to the future health of the NIH enterprise. You stated that it requires the full development of the scientific talents of our entire society, including women, members of underrepresented minority groups and those with disabilities.

This is an area that our subcommittee has had to undertake not only with you but your predecessors over a long period of time. It is regrettable, because we really ought to be able to spend our time on other matters related to the budget. However, we must address the problems of racial discrimination and the lack of opportunity for all groups.

I note that you have hired Clifford Alexander and Associates to develop a comprehensive program to address the problem. Can you tell us when you anticipate a report or some action relative to the action to be taken by Mr. Alexander?

He is a very competent individual, highly qualified in this area, and he should produce some excellent results for you.

Dr. VARMUS. Mr. Alexander has already been active and has helped me on a number of discrimination matters. He has been advising us about our soon-to-be-issued manual on reprisal and has undertaken with his associate, Janet Hill, a large-scale study of our intramural program.

He has a one-year contract. He is expected to provide an interim report to us. He has come to meetings of our ICD Directors, and he has been advising me with great frequency about the matters you brought up.

Now he is in the process of reviewing, in its entirety, our intramural program. It is a difficult, complicated business, but we expect to have specific recommendations from him about how we can increase the proportion of minorities in our work force very soon.

REPORT ON RACIAL DISCRIMINATION AT NIH

Mr. STOKES. In the Conference Report that was adopted for the fiscal year 1994 bill, we included language stating that the conferees are concerned about serious charges of racial discrimination and sexual harassment at the National Institutes of Health. The problems should be addressed and resolved. The conferees instruct the Secretary to submit progress reports on the resolution of this problem to the House and Senate committees semiannually, with an initial report due not later than January 31, 1994. Are you aware of this language?

Dr. VARMUS. Yes.

Mr. STOKES. Has that first report been complied?

Dr. VARMUS. It was recently submitted this week to the Public Health Service, to the Assistant Secretary for Health.

Mr. STOKES. So in terms of compliance with the January 31, 1994 date, that has not been complied with?

Dr. VARMUS. That is correct.

Mr. STOKES. When do you anticipate that this provision of the conference report will be complied with?

Dr. VARMUS. Well, the report will have to go through clearance in the Department. We can make some phone calls and try to expedite the report.

EXTRAMURAL CONSTRUCTION

Mr. STOKES. I would appreciate being advised as to when we can anticipate that progress report.

Also in the conference report, language was included stating that 25 percent of the $7 million provided for extramural facilities construction ought to be awarded to institutions of emerging excellence. What is the status of the 25 percent allocation?

Dr. VARMUS. I am consulting with my colleagues, trying to get the answer to that question. We could provide that information for the record if you like.

I am told it is under peer review at the moment, Mr. Stokes.

Mr. STOKES. Do you have any idea, any indication as to when these awards will be made?

Dr. VARMUS. If it is under review now, the awards will be made by September 30th.

Mr. STOKES. All right, do you anticipate that that provision of the conference report will be complied with?

Dr. VARMUS. We anticipate that.

Dr. KIRSCHSTEIN. Through the National Center for Research Resources.

IDENTIFYING AIDS RESEARCH PRIORITIES

Mr. STOKES. Dr. Varmus, how does the NIH Office of AIDS Research make funding decisions for the AIDS trans-NIH area? How are research initiatives identified, what criteria are used to select projects for funding, and how are funds allocated under this trans-NIH area.

Dr. VARMUS. Sure.

As I just indicated to Mr. Porter, the budget is formulated and, of course, projects identified by the work of five coordinating committees that represent the five major broad disciplines in AIDS research. That is vaccines, therapies, pathogenesis, epidemiology and behavioral research. The committees are composed of NIH scientists and administrators, and we bring in a large number of extramural investigators as well to provide us with advice.

Dr. Paul and his office, which is growing as we speak, then, listens to these various committees. Additional conferences are held. There is consultation with Institute Directors and with me. Finally, the budget is formulated by Institute in accord with both ongoing and new initiatives.

You must remember that, as in all phases of NIH research, we have a fairly substantial commitment base, so that roughly 70 to 80 percent of the money that we receive each year is used to support ongoing activities that are dictated by commitments we have made for multiyear support of grants.

OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. STOKES. Does the Office of Research on Minority Health function in the same manner as a trans-NIH office?

Dr. VARMUS. In many ways it does. The Office of Research on Minority Health has a substantially smaller budget than the Office of AIDS Research, and much of its money is used to supplement minority-related projects in a wide variety of Institutes.

And Dr. John Ruffin, who is in charge of that office, has made an extraordinary effort to identify projects and to encourage new projects throughout the other Institutes.

As you know, Mr. Stokes, from our recent meeting in Chicago, he has sought the advice of many in the minority communities, both researchers and clinicians, to identify regions and areas of research that may be neglected or underfunded to attempt to stimulate interest in those areas on the part of the Institutes. So most of his funding is a collaborative effort between the various ICDs and his own office.

COMPARISON OF ORMH AND OAR

Mr. STOKES. I am aware of many of the activities that particular office conducts. I am highly appreciative also of the high-caliber work that is done from that office through Dr. Ruffin. I am however a little concerned about whether or not that office is permitted to operate the same way as the AIDS trans-NIH office does.

For instance, how does the Office of Research on Minority Health identify its priorities for minority research and research training?

Dr. VARMUS. Some of the mechanisms are really quite similar. Dr. Ruffin has held a series of regional meetings with those interested in minority health and minority health research to identify areas of concern. He meets with representatives of the various Institutes to examine their research portfolios and look for opportunities to increase support.

The proposed FY 1995 budget for the Office of Research on Minority Health is $10 million. The Minority Health Initiative received $56 million in 1994 and will receive an additional $10 million in 1995. In total, including minority programs supported by NIH ICDs, NIH expects to commit $1.1 billion to minority health and assistance in FY 1995. In contrast, the Office of AIDS Research will manage all NIH AIDS research efforts with a budget of $1.378 billion for fiscal year 1995.

But the principles I think are extremely similar, and the allocation that goes to his Office through the Minority Health Initiative is money that can be disbursed widely through the Institutes and used to stimulate interest and excellence in a wide variety of research projects in virtually all Institutes.

Mr. STOKES. When the Office of Research on Minority Health provides funds to NIH Institutes, Centers and Divisions, do these funds typically augment existing minority programs or efforts or do they replace funds previously provided by the Institutes, Centers and Divisions?

Dr. VARMUS. They typically augment, but in some cases they help initiate new projects. There is also quite a substantial investment in training programs, especially innovative training programs.

Mr. STOKES. Is this the same way the AIDS Office operates in that respect?

Dr. VARMUS. Well, the AIDS office has a much smaller investment in training programs.

Mr. STOKES. Does the Office of Research on Minority Health have the authority and the resources needed to carry out its multiple responsibilities?

Dr. VARMUS. Well, I felt that this is an area that has been somewhat neglected in the past, and for that reason I have asked for and have received in the President's budget an increase for funding in that office. It was a substantial increase in FY 1995 of $10 million over a previous base of $56 million for FY 1994. I think there is an opportunity to spend more money wisely in this area.

Mr. STOKES. Thank you, Dr. Varmus.

Thank you, Mr. Chairman.

Mr. SMITH. Mr. Bonilla.

DISCRETIONARY SPENDING LIMITS AND RESEARCH FUNDING

Mr. BONILLA. Thank you, Mr. Chairman.

Dr. Varmus, first of all I would like to associate myself with some of the comments my colleagues made earlier. We are fortunate to have you running the NIH now, and I appreciate the assertiveness that you have taken to meet with us privately about some of the issues involving funding for the next year and in future years for the NIH. We appreciate that very much, the extra time that you are taking to let us know what is important at NIH.

One of the first things I would like to ask is just about the overall budget. The increase is a little over 4 percent. How will this effect the 50,000 scientists that work with NIH?

I know that is a broad question, but I want you to refer to things like expanded research. Are they optimistic about that? And how does it affect the scientists as well in their area of morale? Are they happy with that? Is it going to motivate them? Is it going to offer great hope for the future? So if you would answer that in a broad term.

Dr. VARMUS. Well, as you know, Mr. Bonilla, we are asking for an increase that is just slightly ahead of the inflationary rate. Therefore, this is not an era of maximal expansion.

The scientific community is realistic. Their heads are not buried in the sand. They know we have discretionary funding caps and of the other demands upon the Federal budget. In general, I think scientists are appreciative of Secretary Shalala's enthusiasm for NIH, and President Clinton's commitment to keep NIH ahead of inflationary rates despite the cap on discretionary spending.

In addition, in recognition of the restraints on spending, a number of scientists in the academic community have been enterprising in finding other means to help fund research. For example, collaborations between academic scientists and industrial concerns have allowed the development of cosponsoring of research by the Federal Government and industry that has worked in most cases to the benefit of the investigators. There has been increased dependence upon voluntary organizations as a source of funds, and upon the Howard Hughes Medical Institute and other organizations.

I would prefer that such requirements for identifying alternative sources of support to expand research at this time of remarkable opportunity not need to be sought, but I think there is recognition that there are restrictions upon us, and the signals that are being sent by the administration I think are viewed as positive by my colleagues. Most of them, of course, would like to see a higher degree of enthusiasm and a higher budget line, but there are realities that they are willing to accept.

SUPPORT FOR YOUNG INVESTIGATORS

Mr. BONILLA. What about young people out there who aspire to be in your line of work, which is very exciting. What are you hearing from some of the medical students out there that are hopeful of entering your line of work? Are they seeing the budget constraints as a problem and perhaps turning their interests or are you seeing no change at all?

Dr. VARMUS. Well, there is no doubt that success rates that average around 24 percent, but can be as low as 10 to 15 percent in some areas, send a signal of challenge, if not concern, to young investigators interested in doing Federally-funded research.

It is also the case that investigators who are being trained in labs such as my own are aware of many new opportunities in science other than the path followed by people like myself who received Federal support for most of my career. Among the avenues they are following are opportunities to work in biotechnology companies, that support many thousands of scientists and do excellent work, both in basic and applied research; in pharmaceutical houses; in education; in patent firms; and in many other areas of activity that have been spawned by the remarkable revolution that has occurred in biomedical research in the last couple of decades.

Mr. BONILLA. I certainly hope that all those young students share your optimism and that is your message very strongly, and it is good. But I hear from some of my teaching hospitals—like UT

Health Science Center in San Antonio—that there are some concerns. So I hope that somehow your optimism can be translated downward.

Dr. VARMUS. I hope you heard the complexity of my views in my statement. I recognize the importance of this issue.

Mr. HOYER. Subtlety is sometimes a problem.

PENALTIES FOR RESEARCH FRAUD

Mr. BONILLA. In light of the money problems that we are all experiencing, I want to ask you the same question that I asked Secretary Shalala last week about the Canadian researcher, I believe his name is Roger Poisson, who was involved in fraud in a breast cancer research project. And as a result, the Office of Research Integrity at HHS is barring him from receiving any U.S. Federal research grants for eight years.

I know this topic also came up before Chairman Dingell, and you testified along with Dr. Broder from the National Cancer Institute.

My question is, why would he not be barred for life? Why only eight years? When something malicious like this happens and it was intentional, it is unacceptable. This is a crime that was committed. Why would he be considered at any time in the future for a research grant?

Dr. VARMUS. Well, Mr. Bonilla, I sympathize with your desire for maximum penalty.

As I understand from my conversations with the Director of the Office of Research Integrity, the maximum penalty, the maximum disbarment is 10 years, and he received nearly the full extent of the penalty. The likelihood that Dr. Poisson will ever again be funded by the NIH I would say is remarkably close to zero. It is remarkably hard to take a sabbatical from research for eight years and reenter the fray, especially with a reputation like the one Dr. Poisson has developed.

We are attempting to take other kinds of actions to recover from the outrage of his actions. We are trying to recover the grant money that was expended at St. Luke's Hospital in Montreal through the Justice Department and through our connections with law officials in Canada.

Mr. BONILLA. My next question was about attempts to recover the $1 million in funding for his research. I am glad the attempt is under way. I think the message needs to be loud and clear to everyone that this kind of——

Dr. VARMUS. But as you realize, Dr. Poisson's actions were intolerable, but they were not the only point of difficulty in that episode. We have other fish to fry.

INDIRECT COST PAUSE

Mr. BONILLA. Lastly, I would like to just ask about the pause that the Chairman referred to earlier, indirect costs of research that institutions bear, and the idea of delaying it for a year to save, I believe, $130 million. Doesn't this punish success by penalizing successful and expanding research institutions?

Specifically, I talked to you privately about the UT Health Science Center and the UT system, and projects that may be under way already where they are able to build a new lab, and they have some utility bills that they budgeted for the coming years. And when you cross every T and dot every I and do everything right and you are able to surge ahead, suddenly the pause threatens to yank your chain and pull the rug out from under you for things that you may already be budgeting for the next couple years.

Dr. VARMUS. Well, the pause, first of all, will only affect about $80 million—in outlays—of NIH support. It would not reduce levels of indirect cost reimbursement. It would only restrict any increase in funding of those institutions that are already receiving as much as $10 million in indirect cost reimbursements each year. The pause is intended for one year only.

As has been mentioned more times than I can count in this hearing already, we are operating under severe budgetary restrictions, and this has been viewed by the administration as one way to share the pain. None of us enjoy this process, but it is a way to attempt to engage all components of the research enterprise in the restraint that is necessary. But it would not reduce the amount of indirect cost reimbursements.

Mr. BONILLA. What do you say about the Congressional Budget Office reaction that the freeze would not produce any savings until fiscal year 1996 instead of this fiscal year?

Dr. VARMUS. That is not in accordance with the analysis that I received from the Department.

Mr. Williams might want to comment. Mr. Williams is from the Department Budget Office.

Mr. WILLIAMS. I am not actually personally aware of the study, although I will be glad to look into it.

The way the budget is set up for indirect costs the pause would effect, actually, outlays from prior obligations that are available to universities if they were to exceed their indirect cost rates in fiscal year 1995. So we believe that the mechanism is in place to actually achieve the outlay savings that are estimated in the budget.

Mr. BONILLA. I would appreciate your looking into the CBO report and getting back to me on that.

Thank you, Dr. Varmus.

Thank you, Mr. Chairman.

[The information follows:]

DHHS COMMENTS RELATED TO THE INDIRECT COST PAUSE

We understand the Congressional Budget Office scored all outlay savings from the proposed "pause" in FY 1996 because most universities would not know the increase in FY 1995 indirect costs over the FY 1994 level until very late in FY 1995. The Office of Management and Budget believes that outlay savings associated with the pause can be achieved in FY 1995. I would also note that the House's version of the FY 1995 Budget Resolution assumes $130 million in outlay savings from indirect costs.

Mr. SMITH. Mr. Hoyer.

Mr. HOYER. Thank you, Mr. Smith.

EFFECT OF FTE REDUCTION ON NIH

Doctor, I also want to welcome you to the committee and to your position. You obviously come with very, very high standing among your colleagues, and clearly you have come into what has to be one of the most exciting jobs in your profession in the world at a time, as you point out, when it appears that we are on the brink of many exciting scientific discoveries.

Let me mention some preliminary questions that came up from your answers.

About the 252,000 FTE reduction: what ramifications does it have specifically at NIH given that many of your senior-level staff are, as you've pointed out, scientists who run labs?

Dr. VARMUS. Well, we have been asked to reduce our work force in a way that has required us to eliminate roughly 700 positions in the last three years. About 500 of those have come from our research series and about 100 from research management and support.

Our difficulty is experienced particularly at the highest levels.

Mr. HOYER. Doctor, when you say research series, would it be accurate to say you've lost 500 researchers?

Dr. VARMUS. They aren't all researchers, but they all serve the research activities of NIH.

We are particularly encumbered by the restrictions or the demands for reduction at the higher levels, GS–14, GS–15, and our senior executive service and senior scientific service positions. Those are positions that have been targeted for a particularly high rate of decrease, 10 percent over the next several years, because in many components of the government those positions are occupied by managers just below the top levels who are considered to multilayer the administrative process.

At NIH, most of those positions are held either by individuals who have responsibility for an entire research program in the extramural community or by scientists who have a laboratory with some post-doctoral fellows and trainees and perhaps a technician or two and are doing research in one specific area.

So when we eliminate one of these positions we eliminate not just one person who may spend some money and pass out some orders; we are eliminating a person who represents a program for research or administers a program for research in the extramural community. So, we are not talking simply about people, we are talking about programs, as well.

Mr. HOYER. Doctor, let me interject there. Would the presumption be that somebody who handles X number of project grants would handle X plus Y number, taking up the slack from those who had left?

Dr. VARMUS. That would be necessary. If it can't be done, we would have to decrease the number of grants that we can handle in our portfolio.

Mr. HOYER. But the proponents of a "rational reduction" in the federal workforce, would argue in fact you are not reducing the research grants, you are simply reducing the administration of them.

Dr. VARMUS. But it is simply not possible for our grants managers, who already work extremely hard, to be given additional responsibilities. The oversight of our research portfolio would fall.

As you saw from the charts that we showed earlier, although the budget of NIH has increased dramatically we have not increased the percentage of our funds that we allocated to research management. It has actually fallen slightly over the years. So we have folks who are working extremely efficiently, and it is difficult to imagine stretching them further.

I should also point out that one of the reasons we have this particular situation is that the intramural program of NIH has been judged an administrative expense as opposed to a scientific activity. If we could reverse this judgment, we would perhaps be able to modify the reduction that we are being asked to take in these higher level positions.

Mr. HOYER. Doctor, how would you envision that working?

Dr. VARMUS. We have asked for a 5 percent rather than 10 percent reduction in these higher level positions, which will be more in accord with the activity of people who are in those positions. We will be happy to provide the numbers for you for the record.

[The information follows:]

SENIOR LEVEL EMPLOYEES OF THE NIH

Of its Full-time equivalent ceiling of 16,804, NIH supports approximately 2,900 employees in the Executive, Senior Executive Service, Senior Technical, Senior Level, and GS 14/15 positions. Of this number approximately 1,400 are employees with non-supervisory responsibilities, principally scientists from NIH's intramural research program, and to a smaller extent, Health Science Administrators with responsibility for providing oversight for extramural awards.

Mr. HOYER. Doctor, secondly, equitable workplace. Let me just comment that I am sorry I missed the meeting you had recently with my colleague, Mr. Stokes on this crucial topic. Equal opportunity problems continue to present a particular challenge at NIH.

First of all, the pool of possible recruits in the minority fields has been probably smaller in terms of basic biomedical research. But, clearly, enough effort has not been made in that area, and on a broader scale in terms of nonscientific, nonmedical personnel at NIH. And I am pleased to hear, in your responses to Mr. Stokes, that you have a commitment to tackling this challenge.

OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES

Let me ask an additional question in the three or four minutes I have remaining. Basic and applied behavioral research: almost a year has passed since the Office of Behavioral Research was authorized. I am curious how it is progressing, and, more generally, I would like to hear your vision of the role of behavioral and social science at NIH.

Dr. VARMUS. Well, as you know, Mr. Hoyer, we have a major investment in the area of behavioral and social sciences. Roughly $880 million is being spent in FY 1994 in that area. In the AIDS area alone we are spending about $170 million.

The Office of Behavioral and Social Sciences that was mandated by the Revitalization Act has a charter. It is, I believe, still awaiting final approval. We are at the verge of initiating a search for a Director of that Office. I expect the Director will be an outstanding behavioral or social scientist who will be able to coordinate the activities of behavioral scientists in all of our Institutes and to provide advice and supplemental funding of the major initiatives we have under way.

Mr. HOYER. How useful do you think that is?

Dr. VARMUS. At this point, since behavioral research is a discipline that affects so many of the diseases that we study and has not been coordinated in any sensible way, I think it will be extremely useful to have someone who is providing oversight over this discipline.

Mr. HOYER. I haven't phrased the question in that context, but we have heard about a possible prevention research initiative for NIH as part of health reform. Could you comment on that briefly?

Dr. VARMUS. Well, Title III of the Health Security Act provides for a prevention initiative, of which NIH is, at least in some versions of the bill, intended to be an explicit beneficiary.

There are many kinds of prevention research. There is, as I described in my opening comments, one kind of prevention research that derives from the identification of colon cancer genes and our new-found ability to identify those folks who are at risk, particularly high risk of colon cancer. We expect to obtain very similar information for breast cancer in the near future.

Where we have screening devices for prevention, we can make major strides simply by doing genetic testing and providing colonoscopy for those who are at risk for colon cancer.

The behavioral issue then becomes one of convincing people to be tested, convincing them to appear for colonoscopies on an annual basis. These are extremely important issues because it is one thing to define a medical opportunity to prevent disease and another to convince the population at risk that it ought to receive the benefits of the medical research that we have done to make the prevention strategy possible.

So it is very hard for me to imagine proceeding with traditional biomedical approaches to prevention without a behavioral component that allows us to understand what brings patients in to take advantage of the prevention strategies that are now possible.

Mr. HOYER. Thank you, Doctor. I have other questions. I will ask them later if I have an opportunity.

Mr. SMITH. Ms. Pelosi.

Ms. PELOSI. Thank you very much, Mr. Chairman.

Mr. Chairman, as you may know, Dr. Varmus is a source of great pride to us in California, coming from the University of California, San Francisco, Medical School. I believe our country is well served by his being at the NIH, and I am pleased to see he has made the transition from eminent Nobel Laureate researcher to administrator with great ease.

Dr. VARMUS. Appearances are deceptive.

Ms. PELOSI. The Chairman said people are leaving California in droves. I don't think that was the motivation. I think that coming before this committee was perhaps part of it.

I also wish to commend Dr. Bill Paul and congratulate him on accepting the position of the Director of Office of AIDS Research. Secretary Shalala indicated last week Dr. Paul comes to his office with outstanding credentials and the full support of the administration, which is very important to the issue you are there to serve. And, indeed, welcome to the entire NIH team.

Dr. Varmus, I want to associate myself with the remarks of my colleagues, Mr. Stokes and Mr. Hoyer, in terms of the equitable workplace that they mentioned as well as the research in neglected areas that you referred to as neglected aspects of health of women and minority populations. I appreciate your reference to that as Mr. Stokes indicated earlier as well. I think that is very important.

I appreciate coming later in the game because some of my questions are asked and I can get down to some finer points of interest.

OFFICE OF AIDS RESEARCH

Last week, Secretary Shalala spoke in strong support of the Office of AIDS Research reforms found in the NIH reauthorizing legislation. I appreciate the response that you gave to Mr. Porter about the justification for AIDS research, scientific opportunity, medical urgency, the fact that that is infectious, et cetera, but I wonder if you could comment on the ways in which the consolidated AIDS research budget and strategic planning process may improve the planning and management of federally funded AIDS research.

Dr. VARMUS. Well, I have been watching over Bill's shoulder as he goes through this process, and actually spent a whole day participating with him as a number of distinguished colleagues from around the country came to NIH to comment on the planning process. Although I have not been intimately associated with other planning processes in other Institutes to date, I have been impressed with the thoughtfulness that has gone into the reevaluation of all aspects of our attack on AIDS.

There is no doubt that having the opportunity to assemble five coordinating committees, to staff those committees with distinguished scientists and to call upon the extramural community for new ideas and to have fresh blood represented by an individual as thoughtful as Bill Paul is going to have an effect on the way in which we approach this disease.

There are many scientific subtleties to this disorder. We know the cause, but we don't understand how the virus interacts with the immune system. There is an enormous amount of information available about the virus itself. We are learning tremendous amounts about the proteins the virus makes, and we are learning things that have great impact on other areas of science from our attempts to take this virus apart.

But we still don't understand the most fundamental aspects of how the virus undermines the function of the immune system. Attention paid to those issues is going to have a dramatic impact on our understanding of AIDS, and I think that the accumulated past experience we have gained from Tony Fauci and the new surveillance provided by Bill Paul and his colleagues will have a major effect on how we plan to attack this disease in the near future.

Ms. PELOSI. I look forward to asking Dr. Fauci about that I believe tomorrow.

But I wonder if you could today describe the committee's coordinating structure and how the planning groups are setting priorities.

Dr. **Varmus**. Yes, certainly.

By mandate, the committees are composed of representatives of the Institutes with major investments in each of the five research areas originally designed by Tony Fauci, which are, as I mentioned earlier, epidemiology, pathogenesis, therapeutics, behavioral aspects, and vaccines. Each Institute that supports research endeavors in these disciplines is represented at the table by one person from the intramural program and one who has oversight for extramural grants.

In addition, Dr. Paul has invited to the meetings of the coordinating committees, which occur at least annually, representatives of the extramural scientific community who have expertise in each of these areas.

About a month ago, the five committees met and about 120 to 130 people were on hand to conduct the evaluation of existing programs, decide which areas should be strengthened, and which areas should be scaled down. Subsequently, as I mentioned a moment ago, Dr. Paul invited a number of other individuals to deliberate about the findings of the coordinating committees and the priorities which they had established.

These committees are abetted, I should say, by the wise consultation with members of the activist community who have provided divergent views about how the money should be spent and what the priorities should be in the five areas. So there is a very wide consensus-building process that I think has served to establish the AIDS budget for 1995 and will be, of course, used to develop the 1996 budget as well.

AIDS DRUG DEVELOPMENT

Ms. **Pelosi**. Thank you, Dr. Varmus.

One more question. Dr. Varmus, what consideration are you currently giving, if any, to different mechanisms to manage AIDS research which may be more product oriented? As you may know, Dr. Kessler has said that there is no drug in the approval process.

Dr. **Varmus**. Yes. Well, I am a member of the AIDS Drug Development Task Force that is now chaired by Dr. Philip Lee, the Assistant Secretary for Health. That task force met in Virginia last week. Dr. Paul and Dr. Fauci were both with me.

The group, which includes components of the activist community, people from pharmaceutical companies, people from government, people from academic institutions, of course, could not escape the unfortunate conclusion that there are not a lot of drugs in the pipeline, but there were some new developments that were of interest.

For example, pharmaceutical companies announced that a consortium that they had developed under the leadership of Ed Scolnick of Merck about a year ago has come up with an innovative trial of multi-drug therapy beginning in the very near future. And a number of new initiatives for identifying difficulties with drug development and subcommittees to look into those potential obstacles to drug development were discussed during the course of the meeting.

I think the meeting, although sober in tone, also identified a number of barriers. That was the intention of Secretary Shalala when she put the task force together.

Ms. PELOSI. So the mechanism would be the task force? I appreciate what you are saying, and there is a little more reason to be hopeful, but I just wondered if there was any different mechanism to manage research.

Dr. VARMUS. Well, I think what is being envisioned in this task force is an opportunity to examine the various components of the research enterprise—that is, government, industry and academia—and to attempt to bring those components into more frequent interaction to identify research opportunities that might be missed because there are either administrative obstacles or some lack of collaborative spirit among these various components.

And with the advice of people like Dr. Lee and AIDS activists who are participating on the committee, we are hoping to do the best we can to strengthen this collaborative spirit. There is no substitute for someone at the research bench making a discovery. That is where it happens. But this is a useful way to try to make things work smoother at the research bench and to ensure that basic research discoveries get translated into action.

Ms. PELOSI. I asked, as you know, because of interest in the team approach to developing in a more product-oriented way.

Dr. VARMUS. Well, there are team approaches already under way.

Ms. PELOSI. Thank you very much, Dr. Varmus.

My time is up. Thank you, Mr. Chairman.

Mr. SMITH. Ms. Lowey.

Mrs. LOWEY. Thank you. I am so glad there are so many doctors in the house since my voice is practically gone.

Dr. VARMUS. They won't be able to help you.

Mrs. LOWEY. Please bear with me. It is getting worse and worse.

Mr. SERRANO. Can't hear a word you are saying.

Mrs. LOWEY. I can't, either.

Mr. HOYER. Research, deep research and billions of dollars later, ought to take two aspirin and go to bed.

Mrs. LOWEY. I can't miss the opportunity, though, to welcome you and your colleagues here today. And I want to share my colleagues' enthusiasm for the important work of the NIH. As we debate health care reform, I know that my colleagues share our commitment to ensuring a strong NIH because, in the long run, that is really the key. So we want to thank you for your important leadership.

I also want to respond to some previous comments.

I agree that we must reserve the flexibility of the NIH to conduct and support basic research. I believe it is critical that the NIH does focus its resources on basic research. However, I also applaud your support for addressing concerns that have been neglected for far too long, and that is women's health, minority health, environmental health, and other areas.

So I do want to second your views that it is important to keep all this in balance. While we have to maintain strong support for basic research, I think there has to be an understanding that we have to address those areas that many of us feel have been neglected.

INVESTMENTS IN BIOMEDICAL RESEARCH

My first question concerns the portion of the Federal government's investment in biomedical research and development. It has declined over the past 10 years from 38 percent to 32 percent. Total government expenditures as a portion of the total expenditures also declined by a similar amount during that time. Meanwhile, overall investment rose substantially, due largely to rising support from private industry.

I am interested in that balance and your view of that balance. Do you see any problems arising from the growing predominance of industry-sponsored biomedical research? If you could set the percentage of NIH's contributions to the Nation's investment in biomedical research, what percentage would you choose? What is the optimal mix between government-sponsored research, other government-supported research, and privately funded biomedical research? Perhaps you could comment.

Dr. VARMUS. Well, you raised a series of very difficult problems.

Yes, of course, in asking industry to sponsor biomedical research in the universities we are providing not only opportunity but also danger. And we have been addressing, through a series of panels, the nature of the interaction and how abuses may arise in the context of cofunding. There is the danger of loss of intellectual freedom. There is the risk of undervaluing government investment in academic research.

And yet the general consensus at the moment is that, under the provision of the Bayh-Dole Act, for example, that the interactions that have occurred between the academic and industrial sectors have been working quite well. There are a few exceptions that have been noted in the press and elsewhere that have been cause for concern, but we are hoping that, with negotiation, we can work some of those out.

The appropriate numbers for the amount of money that should be invested in research from various sources is one that I find a little difficult to deal with on short notice.

Mrs. LOWEY. Probably just the more the better, right?

Dr. VARMUS. Well, but you are asking about the balance, and that is an important question. And, of course, it is always difficult to know what the boundaries are in deciding about industrial support for research. Is pharmaceutical money for development of a drug the kind of research we are talking about? And I find those numbers hard to integrate into a notion of how the NIH will conduct its affairs.

It is useful for us to look at an indicator of whether enough money is being provided to support basic biomedical research and behavioral research at NIH by gauging the kinds of applications for research that are not being funded. When we turn down outstanding investigators who have been through many years of training and have proposed excellent projects that we think would advance the Nation's health, then it is quite clear that we have not achieved a level of funding that is suitable for the environment we have created with our investment over the previous decades.

So I find that argument, which is concrete, much more accessible to this kind of discussion than an abstract notion of where the money should be spent across the government.

BREAST CANCER ACTION PLAN

Mrs. LOWEY. Thank you.

I wanted to follow up on my questions last week to Secretary Shalala regarding the Breast Cancer Action Plan. You indicated that the NIH will work in conjunction with the Centers for Disease Control to carry out a wide range of actions related to breast cancer as called for in the Action Plan. I understand that the Action Plan also anticipates a role for the Office of Women's Health, which is located at the Office of the Assistant Secretary for Health, which would work to coordinate various parts of the Breast Cancer Action Plan.

How do you expect the NIH will interact with the Office of Women's Health in coordinating its action with our other aspects of the Plan?

Dr. VARMUS. Well, as you point out, there are multiple components to the Plan.

First of all, we have a major investment overall in breast cancer research, which I should point out involves a wide variety of disciplines ranging from clinical research to behavioral research to basic research in cell biology and genetics. Each of those components is important and largely coordinated through the various Institutes of the NIH, particularly NCI. Many others as well, have investments in research that have a direct bearing on this awful disease.

The Action Plan, which is the outgrowth of a conference that the Secretary sponsored in December at NIH, is an NIH allocation of $10 million which, as you point out, will involve a collaboration and distribution of funds between the NCI and the CDC. We will also be interacting with Dr. Susan Blumenthal who is the new Director of the Office of Women's Health in the Assistant Secretary's office.

To date, interactions between Dr. Broder and Dr. Blumenthal have been frequent and gratifying. We expect that direct communication will continue to flourish between the two Offices. Since these Offices interact directly with each other it shouldn't be difficult to maintain appropriate communication.

Money is being spent by us and by the CDC, but we expect to have useful input from the Assistant Secretary's office.

WOMEN'S HEALTH INITIATIVE

Mrs. LOWEY. Thank you.

I am also pleased to see the NIH has requested the full $61 million necessary to continue the historic work of expanding our understanding of women's health under the Women's Health Initiative.

The Institute of Medicine, as you know, last year issued a report on the Women's Health Initiative that recommended a number of changes to the project. What can you tell us about the NIH's effort to respond to that report? And, in doing so, are you maintaining the original goals of the Women's Health Initiative?

Dr. VARMUS. When we received that report I called for a meeting of several individuals who had been on the IOM panel as well as several people from our own staff and from the extramural community, who were involved in the formulation of the Women's Health Initiative. We met one long and snowy day in February in a hotel in Bethesda to discuss the various areas in which the Women's Health Initiative had been criticized in the IOM report.

In particular, there were criticisms of the Initiative's participant consent form, which already had been rectified. There were concerns about the budget, a problem on which agreement was soon reached. There were concerns regarding the Initiative's endpoints concerning the length of the study and the need to demonstrate that NIH has established particularly effective data safety and monitoring boards for these studies. We expect to have frequent reviews of the data and to evaluate decisions regarding when the study should be concluded.

All those revisions to the Initiative were met. Thus, with uniform agreement we agreed to go forward with the project.

One area of healthy disagreement was what the outcome, or the endpoint, should be in the diet modification portion of the Women's Health Initiative. The original proposal in the Women's Health Initiative highlighted that breast and bowel cancer incidence as the primary object of interest in the effort to lower the amount of fat in women's diets. This was contested by a number of epidemiologists who believed that the study should focus primarily on cardiovascular disease.

We made the decision to go forward with the study as originally proposed, with frequent monitoring of participants' compliance with the diet, approval of patients into the study, and outcomes in the major categories of the Initiative. The initiative is going forward very much as originally planned, with a tight budget but one that we think is workable.

Mrs. LOWEY. Thank you very much.

Mr. SMITH. Mr. Serrano.

Mr. SERRANO. Thank you, Mr. Chairman.

Doctor Varmus, I also want to join my colleagues in commending you for the work you are doing and certainly for the way in which you answer all of our questions.

Dr. VARMUS. I hope it is this friendly next year. Thank you.

HISPANIC HIRING AT NIH

Mr. SERRANO. It only gets better, I am told by Mr. Hoyer.

As Chairman of the Congressional Hispanic Caucus, Doctor, I come across the concerns of many people throughout the Nation about issues that affect our community, and about getting people to help address our needs.

And last year, with that in mind, the committee report directed the Director of NIH to prepare a plan for increasing the number of Hispanic personnel at the higher levels and to be prepared to discuss the plan and its implementation schedule at these hearings. I would like to know where NIH is in terms of the plan and its implementation at this point.

Dr. VARMUS. Well, as you know, we have been operating under an atmosphere of FTE reductions and, more recently, a hiring freeze. This has impeded our ability to respond to such concerns. NIH has recently hired one Hispanic to an SES level position but NIH has a dearth of Hispanic personnel in those higher levels.

I acknowledge your concern. We have made some efforts to repair the situation. We have hired one Hispanic individual in a recent tenure decision. There has been an increase in our Hispanic personnel from 125 to 198 over the last five years, but only a few of those have been at the SES level and only nine at the GS–15 level.

Mr. SERRANO. Yes, I understand that this is not an easy situation to deal with. But I think, Doctor, you should be aware that these numbers and the inability to bring the numbers up creates a continuing concern about the hiring and promotion of Hispanics at NIH. Charges of discrimination against minorities generally, and Hispanics specifically, persist.

There is also the feeling, at times, that the lack of personnel leads to a failure to address some specific needs. It shouldn't be that way, but there is that concern, and you know that a concern creates a perception. And we are both in a profession where perception, like pitching——

Dr. VARMUS. No, I understand the concern.

Mr. SERRANO [continuing]. Like pitching in baseball, becomes 75 percent of the game.

Dr. VARMUS. I am pleased that one-quarter of my own laboratory staff is Hispanic, but that does not translate into similar levels in all parts of NIH.

Mr. SERRANO. Dr. Rene Rodriguez, President of the Interamerican College of Physicians and Surgeons, has written to me to describe the college's efforts to assist NIH in expanding participation of Hispanics in biomedical research. He sent a copy of the report, Mr. Chairman, which I would like to submit for the record, of the workshop on participation of Hispanics in all phases of biomedical research held last fall and proposed a series of eight steps NIH could take to increase Hispanic participation.

[The information follows:]

STEPS PROPOSED BY THE INTERAMERICAN COLLEGE OF PHYSICIANS AND SURGEONS TO INCREASE THE PARTICIPATION OF HISPANICS IN BIOMEDICAL RESEARCH

To effectively expand the participation of Hispanics in biomedical research NIH should take the following steps:

1. The General Clinical Research Center Program should provide opportunities for biomedical achievement by clinical investigators who do not receive their funding from other components of the National Institutes of Health, and expand its clinical research training and career development to independent clinicians serving underserved and Hispanic populations.

2. The Research Centers in Minority Institutions Program should expand its support to Hispanic research teams in non-minority institutions, since there are no traditional Hispanic colleges in the continental U.S. Also, this program should be expanded to provide more infrastructure development to those institutions with an active Hispanic faculty staff so as to strengthen the ability of those Hispanic faculty groups within non-minority institutions to establish a strong career training research program.

3. The Advisory Councils should promote research in areas which are critical to minority health, and the Division of Research Grants should establish procedures to obtain a wider input for the evaluation of applications in these areas of research.

4. Without affecting the independence of the review process, the Division of Research Grants should discuss new procedures by which an application's relevance to minority health issues would be factored into the decision making scientific review process.

5. The Division of Research Grants should expand the opportunity of Hispanic researchers to participate in study sections, particularly of clinical researchers in institutions serving Hispanic populations, setting the standard by recruiting more Hispanic investigators for its own study sections and review panels, and consider the possibility of inviting Hispanic researchers to provide their particular perspective as non voting reviewers on minority issues. The executive secretaries of study sections should establish links with Hispanic professionals organizations in order to identify qualified reviewers within the Hispanic community.

6. Under the guidance of the Division of Research Grants, NIH should fund a Task Force composed of Hispanic extramural associates, Hispanic professional organizations, and NIH scientific staff to provide assistance to Hispanic professionals in biomedical sciences who are preparing research applications with potentially important implications in minority health.

7. NIH should review the procedures used to promote programs that support the development of minority professional scientists. Reliance on traditional channels within institutions has not been effective in enlisting Hispanic professionals into the NIH research system. NIH should establish links with professional Hispanic medical associations formed within academic institutions and with prominent Hispanic researchers to disseminate and promote the opportunities in biomedical training for scientists.

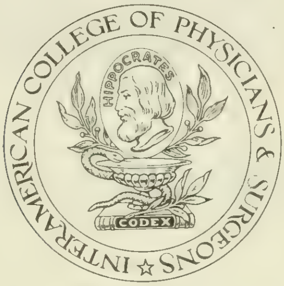
8. The Director of NIH should work with the NIH Hispanic American Advisory Committee, the members of the National Confederation of Hispanic Medical Associations, the leaders of Hispanic Centers of Excellence and Hispanic faculty at medical schools in the identification of Hispanic health professionals, and in the promotion of Hispanic workforce at NIH. In order to facilitate the recruitment of Hispanic biomedical researchers and administrators in its workforce, NIH should support the development of an Hispanic health care providers and biomedical researchers database to network qualified Hispanic researchers, and to establish links with institutions having a relevant Hispanic staff.

REPORT

to the Office of Minority Programs

Presented to the NIH Director for Minority Programs by the Hispanic Physicians and Research Team attending the Workshop on Participation of Hispanics in All Phases of Biomedical Research

October 1993
Bethesda, Maryland



Organized by the Interamerican College of Physicians and Surgeons
sponsored by the Office of Minority Programs.

Interamerican College of Physicians and Surgeons

REPORT

to the Office of Minority Programs, NIH

Participation of Hispanics in All Phases of Biomedical Research

Research priorities for Hispanics
Study sections and review committees
Clinical research training and career development
Science education
Hispanic Representation in the NIH Workforce Profile
Dissemination of NIH programs and research promotion among Hispanics

October 1993
Bethesda, Maryland

Sponsored by the Office of Minority Programs
National Institutes of Health

INTRODUCTION

In May 1991, the National Institutes of Health Office of Minority Programs (OMP) created a Fact Finding Team (FFT) to recommend ways by which NIH could increase the participation of minorities in all phases of biomedical research. The report drafted by the FFT recommended that the NIH undertake additional data collection among minority groups and develop new and varied research methods and procedures in order to successfully address the health needs of minorities. The report strongly encouraged the inclusion of minorities in all intramural and extramural research projects, including clinical trials of medical procedures, medical devices and new drugs. The FFT report also recommended that NIH support the development of community-based biomedical research organizations by providing early planning grants to form such groups and requiring research institutions to interact with these groups using institutional training grants to support the transition of undergraduate minority research trainees to graduate training, and increasing the participation of minority in all phases of biomedical research. According to the FFT report, the dissemination of NIH data on minority health concerns, study results, programs and opportunities within the larger research and biomedical community is essential to achieve these goals and to achieve ethnic diversity at every level and throughout every Institute.

In recent years NIH has established various programs to improve the representation of minorities in all phases of biomedical research and to improve the representation of minorities in its work force profile. Researchers and Hispanic American physicians have been following these initiatives with interest. Many remain, however, skeptical and concerned by the poor results in filling the educational pipeline to health careers with Hispanic students and by the limited involvement of Hispanic physicians in clinical research and clinical trials as well as in other NIH sponsored programs. Despite the creation of the General Clinical Research Center (GCRC) Program, and the Research Centers in Minority Institutions Program the biomedical research environment has not significantly changed its minority representation by the inclusion of Hispanic researchers. The number of Hispanics in study sections and review committees remains extremely low as it is the case with Hispanic participation in intramural programs and at all staffing levels at NIH, particularly in high ranking research and policy positions.

In July 1993, the Honorable Jose E. Serrano of the U.S House of representatives and Chairman of the Congressional Hispanic Caucus, testified before the Subcommittee on Oversight and Investigations on Post Office and Civil Service on the subject of hiring and promotion of minorities within the NIH. The focus of this testimony was the poor employment patterns within the HHS and, particularly NIH, and on recommendations for correcting the underrepresentation. "The dismal record of Hispanic hiring at the HHS and NIH is unacceptable," the Honorable Jose Serrano said before the Committee. In the fourth quarter of the fiscal year of 1993, NIH had 14,573 employees of which only 231 (1.6% of the total) were Hispanic. Also, of the 4,010 management positions, 1.6% were held by Hispanics, and three Hispanics (1.3% of the total workforce profile) held senior executive service (SES) positions. The average salary of Hispanic SES personnel was lower for others at the same level, $99,333 compared to $104,576 for non-Hispanic SES. As with the lack of Hispanics in high level positions, promotion of Hispanics within NIH is equally abysmal. Of 2,293 promotions made within NIH between FY 90 and FY 92, the average for Hispanics was 34 (1.5% of total promotions made).

The U.S. Congressional House Appropriations Bill HR 2518 points out that "Hispanics continue to be seriously underrepresented at all levels of NIH", and directs NIH to develop a plan for increasing the number of Hispanic personnel at the higher levels and to be prepared to discuss the plan and the schedule for its implementation in hearings on the fiscal year 1995 budget request. The committee expects the plan with Hispanic serving institutions and other outside organizations to identify qualified Hispanic health professionals.

The NIH Hispanic Advisory Committee (NIH-HAAC) issued in September 30, 1992 a critical document entitled "Proposal to Improve Hispanic Amercian participation in NIH programs". Also in 1992 a large advisory panel to the Office of the U.S. Surgeon General issued recommendations to improve Latino health. There is a clear uniformity between the statements made by Congress, the NIH- HAAC and the report to the Office of the U.S. Surgeon General, and this report is consistent with the recommendations of the Fact Finding Team to the NIH Office of Minority Programs. The recommendations issued by these bodies substantially agree in the ways by which NIH could increase the representation of minorities, and particularly Hispanics in all phases of biomedical research as well as within the NIH workforce.

As a member of the NIH Minority Programs Fact-Finding Team and President of the Interamerican College of Physicians and Surgeons (ICPS), a national organization representing Hispanic physicians, Dr. Rene Rodriguez strongly supported the development of plan to increse the participation of Hispanics in biomedical research, and with the sponsorship of the NIH Office of Minority Programs, ICPS organized a conference and a workshop to enable the successful implementation of these recommendations within the Hispanic medical community. The meeting and workshop organized by the ICPS was held on September 30, 1993 with the participation of thirty-five physicians from different regions of the U.S. representing a broad spectrum of academic institutions. NIH representation at the conference included the Director of the NIH Office of Minority Health, representing also the acting director of the NIH, and staff members of the following Institutes: the National Cancer Institute; the National Institutes of Deafness and other Communication Disorders; the National Institutes of Diabetes, Digestive and Kidney Diseases; the National Center for Research Resources; the Fogarty International Center; the National Institutes of Dental Research, the Division of Research Grants; the National Eye Institute; the Clinical Center; and the National Institute of Allergy and Infectious Diseases.

The main purpose of this meeting was to create new links between NIH, Hispanic medical organizations and Hispanic biomedical researchers, to serve as a source for identifying qualified Hispanic professionals, and to produce a report that will help the Office of Minority Programs (OMP) implement the following recommendations issued by the Fact Finding Team on Minority Programs:
The FFT recommended that NIH:

1- Undertake longitudinal data collection studies among the many diverse population groups referred to as "minority groups" in order to better determine those factors that affect the health status and needs of minorities.

2- Develop new and varied research methods and procedures in order to successfully address the health needs of minorities.

3- Continue funding its full array of programs supporting the professional development of minority biomedical scientists as well as evaluating those programs in order to identify their strengths and weaknesses.

After presentations by representatives of the Office of Minority Programs and the Institutes, attendees to the conference were charged with the task of analyzing existing barriers to achieve adequate representation of Hispanics in all phases of biomedical research sponsored by NIH, and to recommend implementation strategies that could have an effective impact on the recruitment and participation in NIH sponsored programs.

Participants were asked to develop a draft report of recommendations to meet critical research needs and human resources in each of the following critical areas:

1. Research priorities for Hispanics.
2. Study sections and review committees
3. Clinical research training and career development.
4. Science education
5. Hispanic Representation in the NIH Workforce Profile
6. Dissemination of NIH programs and research promotion among Hispanics.

The report will identify:

A) Means and strategies to promote NIH programs.
B) Outreach capabilities
C) Hispanic faculty that will help promote and expand NIH minority programs.
D) Hispanic hospital-based physicians that will provide NIH with necessary clinical support to gather data on Hispanic populations.
E) Strategies to expand the participation of Hispanic physicians in clinical trials.

I. Research Priorities Among Hispanics

Policy decision makers within HHS and Congress often set priorities to address the health problems of the U.S. population. Minorities have their own particular priorities. The FFT noted that minority Americans suffer a disproportionate burden of illness and death compared to the predominantly white majority. In 1990, HHS published Healthy People 2000, an overview of the current and projected health status. According to this report Hispanics experience perhaps the most varied set of health issues facing a single minority population. The leading causes of death among Hispanic Americans documents several differences between their health experiences and that of the total population. Unintentional injuries, chronic liver disease, diabetes and AIDS rank higher on the Hispanic list. The cumulative incidence of AIDS among Hispanic women is about eight times higher than among non-Hispanic women and the rate of HIV infection is over six times higher for Hispanics. The prevalence of obesity has dramatically increased in the past five years, and diabetes is especially prevalent among Mexican Americans. Hispanic Americans receive less preventive health care and prenatal care and gastrointestinal infections, particularly among migrant workers, are endemic. The rate of parasitic infection among some sets of farm workers approaches 50 times that of the total population; their life expectancy is 49 years instead of 75 years.

Hispanics face increasing health risk in the three key areas; life span issues, chronic diseases and infectious diseases.

Life Span Issues

Low birth weight and infant mortality are elevated among Puerto Ricans, Mexican Americans, Central Americans and, particularly, migrant workers. Improving life span issues among Hispanics must begin with addressing problems such as fetal alcohol syndrome, fetal drug addiction, and reproductive health. Other problems relevant to Hispanic populations involve dental caries, anemia, sexually transmitted disease and mental health.

Adult concerns such as smoking, obesity and alcohol abuse demonstrate the relationship between life style and health. High incidence of diagnosed mental diseases points out, o n one hand, to the effects of acculturation and, on the other hand, to a lack of culturally sensitive therapeutic interventions. The problem of organ donation in the Hispanic population is both serious and complex. The refusal rate of Hispanics is considerably higher than whites in any major city and Hispanics remain separated from the mainstream of organ donation. Hispanics living in the U.S. have not yet integrated themselves into developing protocols and the process to obtain appropriate solutions.

Concerns of the elderly include inactivity, nutrition, pharmacology and pharmacokinetics

Chronic Diseases

Among these are asthma with higher death rate among Hispanics than among the general population; diabetes (and the relationship of obesity to diabetics) particularly among Mexican Americans, and alcohol related diseases such as cirrhosis.

Infectious Diseases

Sexually transmitted diseases, viral hepatitis and HIV infections, have a considerably higher incidence rate among Hispanics than among the general population.

The attendees to the conference have pointed out some of the existing barriers to an adequate prioritizing of research areas:

(1) Inadequate data collection;
(2) Limited participation of Hispanic health providers and researchers in NIH policy decisions.
(3) Inadequate methods and procedures to analyze and address the health needs of Hispanics.

Data Collection

The ICPS committee has found essential barriers to systematic data collection efforts:

(a) The complexity of the NIH granting process precludes the participation in the data collection effort of community health centers, clinics, private physicians, small and medium sized hospitals that treat a large portion of Hispanic population .
(b) The poor links between these health providers and academic institutions hinders the inclusion of relevant health data on Hispanic populations. Therefore, the committee concludes that the inclusion of relevant data on the health status of Hispanic populations remains largely unknown because of the lack of participation of Hispanic health providers in data collection efforts.

Recommendations:

1. Expand the ICPS database of Hispanic health care providers to include all institutions relevant to the data collection effort.
2. Disseminate this data to academic institutions and research centers and stimulate partnerships among them for epidemiological research.
3. Establish financial and professional incentives for health care providers to collaborate in epidemiological research.
4. Develop and implement mechanisms to train health providers in data collection efforts.

Participants to the ICPS workshop strongly recommend that the OMP take the lead in efforts in improving and disseminating existing databases of health care providers of minority populations and work with the Institutes and Hispanic professional organizations to set standards and procedures for data gathering efforts in Hispanic populations.

Limited participation of Hispanic health providers and researchers in NIH policy decisions.

The ICPS committee has found essential barriers to the participation of Hispanic health providers and researchers in NIH policy decisions and program implementation. The underrepresentation of Hispanics in SES positions, in study sections, review committees, science career orientation, and career development workshops prevents an adequate approach to the understanding of health priority issues in Hispanic populations, since existing data does not reflect the actual health status of this minority.

Inadequate methods and procedures to analyze and address the health needs of Hispanics.

The ICPS committee has found essential barriers to the development of adequate methods and procedures capable of analyzing and addressing Hispanic health issues. The limited involvement in NIH sponsored programs of Hispanic clinicians working in hospital based settings and other health providing institutions in close contact with the Hispanic patient population may be partly the result of rigors in the current scientific review process, and the current procedures to support research centers, which marginates potentially valuable researchers.

The ICPS Committee recommends that:

1. The Research Centers in Minority Institutions Program expands its support to Hispanic research teams in non-minority institutions located in densely Hispanic populated areas, particularly to the Hispanic Centers of Excellence, since there are no traditional Hispanic colleges in the continental U.S..

2. The General Clinical Research Center Program provides opportunities for biomedical achievement by clinical investigators who do not receive their funding from other components of the National Institutes of Health, and expand its clinical research training and career development to independent clinicians serving underserved and Hispanic populations.

3. The Advisory Councils promote research in areas which are critical to minority health and that the Division of Research Grants establishes procedures to obtain a wider input for the evaluation of applications in these areas of research.

II. Study Sections Scientific Merit Review

The panel has found that essential barriers exist to the successful award of applications that have a potential for impacting the health status of Hispanics. As it was pointed out before, the rigors of the scientific merit review process limits the participation of clinical researchers in community health centers, clinics, and other health providing institutions who have not been fully introduced to the standards and process in the competition for grants. Most of these physicians serve a large proportion of the Hispanic population and clearly understand the research priorities for Hispanics but do not know how to prepare a successful application.

Also, the composition of the study sections that largely excludes Hispanics, and are unfamiliar with research priorities for this population reduces the prospects of an award.

The panel recommends that::

1.Without affecting the independence of the review process and the fairness of the scientific merit review of proposals, the Division of Research Grants discusses new procedures by which an application's relevance to minority health issues would be factored into the decision making scientific review process.

2. The Division of Research Grants expands the opportunity of Hispanic researchers to participate in study sections, particularly of clinical researchers in institutions serving Hispanic populations. The panel suggests that the Division of Research Grants sets the standard by recruiting more Hispanic investigators for its own study sections and review panels and consider the possibility of inviting Hispanic researchers to provide their particular perspective as non voting reviewers on minority issues. The executive secretaries of study sections should establish links with Hispanic professional organizations in order to identify qualified reviewers within the Hispanic community.

3. Under the guidance of the Division of Research Grants, NIH should fund a Task Force composed of Hispanic extramural associates, Hispanic professional organizations, and NIH scientific staff to provide assistance to Hispanic professionals in biomedical sciences who are preparing research applications with potentially important implications in minority health.

III. Clinical Research Training and Career Development

The Panel recommends that the NIH reviews the procedures used to promote programs that support the development of minority professional scientists. Reliance on traditional channels within institutions has not been effective in enlisting Hispanic professionals into the NIH research system. NIH should establish links with professional Hispanic medical associations formed within academic institutions and with prominent Hispanic researchers to disseminate and promote the opportunities in biomedical training for scientists offered by the MARC postdoctoral fellowships, the Visiting Scientist and Faculty Fellowship Programs, the Minority Research Supplement, the Minority Clinical Research Programs, the Early Grant and Career Development Awards and the Extramural Associates Program. The Biomedical Research Scientists Program should be used as a model for the development of minority research faculty and a core for the expansion of the Hispanic research groups within non-minority institutions.

In order to improve the participation of Hispanics and create a positive environment for the success of these programs among this minority, the panel recommends that all grantee institutions rely on the support of the Hispanic faculty-staff to improve the recruitment, hiring and advancement of minorities and incorporating them into research projects dealing with minority health concerns. The participation of Hispanic faculty staff and NIH extramural associates in the recruitment process is a way of assuring the success in the future review process.

The Panel recommends that the Research Center and Minority Institutions Program be expanded to provide more infrastructure development to those institutions with an active Hispanic faculty staff so as to strengthen the ability of those Hispanic faculty groups within non-minority institutions to establish a strong career training research program.

III. Science Education

The scarcity of Hispanic students in medical careers is a critical problem. According to the Bureau of the Census, Hispanics comprise 9% of the total population. However the number of Hispanics who completed medical careers in 1987 was under 300. In 1980, Hispanic physicians, mostly foreign graduates, constituted 7.0 percent of all U.S. physicians. This percentage declined to 5.9 percent in 1992, and by the year 2000 Hispanics physicians are projected to decline to 2.3 percent of U.S. population while the Hispanic population is expected to growth to 16%.

In the last decade medical schools and government agencies have implemented programs to assist medical students enter medical training. These programs have not increased, however, the graduation rates of Hispanics which remain disproportionately low when compared to the general population. There is clearly an urgent need to expand efforts aimed at increasing, retaining and graduating Hispanic Medical students in the United States.

The panel recommends that::

The NIH play a leading role in sponsoring programs that improve the scientific skills of young Hispanics in the U.S. with particular emphasis on convincing Hispanic high school students to choose science as a career. NIH should fund at least forty high schools located in densely populated Hispanic areas to introduce middle school minority students to biomedical sciences and explore innovative ways to assist Hispanic scientist to serve as mentors and role models in local school classrooms with high concentration of Hispanics.

The panel recommends that NIH in partnership with medical schools colleges, Hispanic professional organizations and community organizations expand the NIH Minority High School Research Apprenticeship Program and other training programs in order to increse a 100% the number of Hispanic students participating in these programs. The Committee also recommends that NIH support bridging programs that help promising Hispanic high school graduates make the transition to campus life and a science curriculum.

The panel recommends that NIH help increase the transfer of talented Hispanic students with scientific knowledge and skills from two year institutions to baccalaureate programs in the biomedical and the life science at four year institutions. NIH should establish collaborative agreements with community-based organizations and two-year and four-year institutions so that good students can be identified, motivated, mentored and supported in the pursuing a quality science curriculum.

The panel recommends that NIH increases the support for the training of Hispanic undergraduate in the biomedical sciences.

IV. Hispanic Representation in the NIH Workforce Profile

In 1993, of 14,573 NIH employees, only 231 were Hispanic although there is a pool of 39,000 Hispanic physicians and 2,000 biomedical researchers in the U.S. Therefore, the panel concludes that hiring practices are inadequate. The panel recommends that NIH follows the advice of the NIH Hispanic American Advisory Committee, the mandate of the Congressional Appropriations Committee and the recommendations of the Office of the Surgeon General in the identification of Hispanic health professionals to serve NIH. The members of the National Confederation of Hispanic Medical Associations, the leaders of Hispanic Centers of Excellence and Hispanic academic faculty at medical schools wish to be included in formal consultations for the drafting of a hiring plan. These groups could be effective brokers in the identification of qualified professionals.

V. Dissemination of NIH Programs and Research promotion Among Hispanics

The Panel recognizes that NIH produces a large amount of information on research and training opportunities, on national Hispanic leadership initiatives, and on technical assistance to organizations conducting community outreach activities, and offers computerized data base information such as the Physician Data Query (PDQ), and the Cancer Facts. While these materials are readily available they often do not reach those groups that would benefit from these most. It is evident that the current dissemination system is not effective in funneling information to Hispanic undergraduates, medical students, postdoctoral fellows, and community health providers among other potential biomedical researchers. Furthermore, even Hispanic faculty members are unaware of many of the programs offered by NIH. Therefore, the panel notes that reliance on the academic administration is not always the best mechanism to funnel information to faculty and staff of their institutions.

The Panel recommends that NIH utilizes multiple distribution channels such as Hispanic medical publications, Hispanic medical society newsletters, student publications, professional meetings, and other Hispanic informational channels, to ensure that NIH publications reach all relevant audiences including Hispanic students, postdoctoral fellows and subspecialists. The Interamerican College of Physicians and Surgeons as well as the members of the Confederation of Hispanic American Medical Associations, the Student National Medical association (SNMA), the Texas Association of Mexican-American Medical Student (TAMAMS), the Hispanic/American Medical Student's Association (HAMSA), the Boriqua's Student Association and others issue an array of publications that could include pertinent NIH information. The Panel proposes that NIH includes such organizations in its contractual arrangements for dissemination of information.

The Panel proposes to utilize existing mentoring programs such as the ICPS-PHS National Mentor Recruitment Network, now assisting 850 medical students and supported by 500 Hispanic physicians participating in this effort, to disseminate the opportunities provided by the MARC Predoctoral Fellowship, the Research Supplement for Minority Individuals in Postdoctoral Training, the Research Supplements for Minority Research Assistants, the Research Career Development Award, the Physician Scientist Award, and the Clinical Investigator Award. It should also promote among mentees the NIH staff fellowships and the NIH intramural and Clinical Associates Program to prepare new human resources for its workforce.

CONCLUSIONS

In summary, the September 30, 1993 Workshop on Participation of Hispanics in all phases of Biomedical Research intends to make significant progress in achieving the following objectives:

1- To establish new and better contacts between Hispanic leaders of health professional organizations, prominent Hispanic faculty members, ICPS' collaborators and staff members of the National Institutes of Health.

2- To develop channels of communication that will allow Hispanic physicians to obtain information regarding the outcomes of ongoing research and guidelines issued by NIH for the management and treatment of disease on a regular basis.

3 - To coordinate with NIH the dissemination of scientific and clinical information on critical issues to the Hispanic community, and to disseminate among Hispanic physicians more information about NIH financial support, training, and professional opportunities in extramural and intramural activities.

4- To increase the participation of Hispanic physicians in clinical research developed by grantees, and facilitate their recruitment efforts by strengthening outreach capabilities.

5- To help disseminate information that will facilitate access of Hispanic physicians and their patients to clinical trials, and foster the formation of community research groups.

6- To increase the contribution of Hispanic physicians and researchers to the research process and data collection efforts.

The September 30 workshop was critical in (a) identifying the steps that need to be taken to accomplish each of the above, and (b) assembling representatives from the NIH, Hispanic biomedical faculty, community based physicians and members of Hispanic medical organizations who will play a key role helping implement those recommendations made by the FFT and those mandated by Congress.

It is perhaps a first step in assembling a group of brokers and qualified advisors that will help NIH meet its manpower needs. Each of the participants are at the core of a network of influence in their respective institutions and communities, actively involved in mentoring, medical training, in organizing professional meetings, congresses and issuing publications that reach the vast majority of the Hispanic biomedical community in the United States, Latin America and Spain.

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Mr. SERRANO. I would appreciate your responding to these proposed steps for the record, and I look forward to reading your response.

[The information follows:]

NIH RESPONSE TO HISPANIC PARTICIPATION WORKSHOP

The NIH welcomes suggestions from the minority community. Dr. John Ruffin's office, the Office of Research on Minority Health (ORMH) has done a remarkable job soliciting recommendations from various minority groups. Indeed, his Office sponsored the Workshop on Participation of Hispanics in All Phases of Biomedical Research, which was organized by the Interamerican College of Physicians and Surgeons. ORMH provided the necessary support for the Hispanic research community to meet and develop the eight proposed steps to increase the participation of Hispanics in biomedical research.

The NIH commitment to these recommendations is demonstrated by the attendance of Dr. Ruffin and almost 20 Institute, Center and Division representatives at the workshop. I understand that Dr. Ruffin is now discussing the implementation of the recommendations with both the President of the Interamerican College, Dr. Rene Rodriguez, and with the NIH ICDs. The initial success of the Interamerican workshop is encouraging. As a result of the success of the Interamerican workshop, ORMH is now in the process of designing workshops with different minority groups to provide a similar forum for the development of comparable recruitment strategies.

Mr. SERRANO. Also, a group of Washington area Hispanic leaders, called the Capital Area Latino Coalition, has expressed dismay over NIH's handling of a discrimination case filed in 1987 by Dr. Henry Stephenson Perez against the National Cancer Institute. We would also like you to summarize the history and status of this case for the record.

Dr. VARMUS. Yes.

[The information follows:]

SUMMARY OF THE EEO COMPLAINTS OF

DR. HENRY STEVENSON-PEREZ

On August 21, 1987, the Complainant filed complaint NIH-001-87 alleging that:

1. because of his national origin, Hispanic, he was denied tenure in the Biological Response Modifiers Program, National Cancer Institute, on April 27, 1987.

2. because of his national origin, Hispanic, he was assigned duties normally assigned to more junior physicians, such as primary patient care activities.

This complaint resulted in a Final Decision of no discrimination from Dr. James O. Mason, Acting Surgeon General, on September 21, 1989. After the Final Decision was issued, the NCI permanently removed the Complainant from intramural research.

On December 28, 1989, the Complainant filed complaint NIH-001-90 alleging that because of his national origin (Hispanic) and in reprisal for his having filed a previous complaint:

1. his 1988 and 1989 Commissioned Officer Efficiency Reports (COERs) were lowered.

2. he was denied access to his laboratory notebooks located in the Biological Response Modifiers Program (BRMP) laboratories of the National Cancer Institute (NCI) in Frederick, Maryland.

3. NCI failed to give him proper credit for his research in a manuscript entitled "Immunomodulatory Properties and Toxicity of IL2 in Patients with Cancer."

4. the NCI refused to pay for scientific reprints of book chapters authored by him.

5. he was involuntarily transferred in June 1989 from the Naval Medical Oncology Branch (NMOB), NCI, to the Cancer Therapy Evaluation Program (CTEP), Investigational Drug Program (IDP), NCI.

This complaint was joined for processing with complaint NIH-003-90 in which the complainant alleged that because of his national origin (Hispanic) and in reprisal for his having filed a previous complaint:

1. his COER for January 1990 was lowered.

2. his medical consult privileges at the Bethesda Naval Hospital were revoked, jeopardizing his Medical Occupational Reimbursement Benefit (MORB) of $20,000 per year.

3. he was denied a billet in the newly established Research Officers Group (ROG) of the Commissioned Corps (CC).

4. he was transferred from the NMOB to the CTEP in June 1989.

5. he was denied a promotion to a CO-06 in the Public Health Service (PHS) CC; and

6. he received a memorandum on May 9, 1990, accusing him of improperly ordering reprints and charging him with repayment for these reprints.

A Proposed Disposition on these two complaints was issued on February 7, 1994. Within 15 calendar days of his receipt of the Proposed Disposition, the Complainant has the right to appeal this Proposed Disposition to the Director, National Institutes of Health (NIH). The Director, NIH, will review the matter and issue a Preliminary Decision appealable to the Surgeon General. Therefore, the administrative processing of these issues should be completed within 90 days.

In January, Dr. Stevenson-Perez filed a formal complaint alleging that because of his national origin (Hispanic) and in reprisal for his having filed previous complaints:

1. he was placed on three weeks administrative leave while the NCI conducted an investigation of him.

2. he was reprimanded based on the investigation.

This complaint will be accepted and investigated and a Proposed Disposition will be issued within 180 days of the acceptance date.

HISPANIC HEALTH RESEARCH

Mr. SERRANO. Some argue, Doctor, that the shortage of Hispanics at decision-making levels at NIH translates to a lack of attention to Hispanic health needs in NIH's research agenda. What percentage of the NIH budget goes toward Hispanic health issues?

And secondly, perhaps it is more appropriately asked of Mr. Ruffin, but what percentage of the NIH Office of Research on Minority Health budget supports Hispanic health issues?

Dr. VARMUS. We spend about $120 million each year on activities that are clearly identified as Hispanic health. Now, of course there is a great deal of additional investment in research that will affect the Hispanic community, but approximately $120 million is specifically addressed to concerns in the Hispanic community.

I am not sure what the percentage of money in the Office of Minority Health actually goes to Hispanic projects and I could provide that for you for the record.

[The information follows:]

ORMH FUNDING FOR HISPANIC PROGRAMS

In FY 1993, the most recent year for which data is available, ORMH spent $8.4 million of the $49.3 million it had available on research and training programs targeted towards specified minority groups. The vast majority of its budget—$40.9 million—was spent on projects which benefited minorities in general. Of the $8.4 million the ORMH spent on targeted minority programs, $2 million, or 24 percent, was used to fund health and training programs specifically targeted toward Hispanic-Americans.

Mr. SERRANO. Right. Again, and I know you understand but I need to put it on the record, the concern is that the lack of information that you can present to me, our inability to really get to the bottom of how well we are doing in this area, continues to promote the perception that certain areas of concern to us, like diabetes and tuberculosis and the research data needed to attack those problems in our community, are not being addressed in the way that they should be addressed.

Dr. VARMUS. Well, let me clarify, Mr. Serrano. The only information I lack here concerns specifically how much support is directed through ORMH for programs related to the Hispanic population. As I stated previously, $120 million is used to support programs that are readily identifiable to Hispanic health. However, there are multiple projects in the area of diabetes, alcoholism, asthma, mental health, and drug addiction, for example, that specifically affect the Hispanic community.

So we are making considerable efforts, both through the Minority Health Office, and all of the NIH ICDs, to address some of the problems that I know are of concern to you.

DIABETES IN MINORITIES

Mr. SERRANO. Thank you. I was pleased, Doctor, to learn last summer of the agreement for joint support of research between the Office of Research on Minority Health and the National Institute of Diabetes and Digestive and Kidney Diseases. As noted in the announcement, these four jointly funded projects address three health problems found disproportionately in minority populations, diabetes, obesity, kidney disease.

The two diabetes projects include Hispanics, but I was curious about the other two. First, the description of the treatment of obesity project says, "virtually every population of minority women is highly impacted by its serious health consequences." But the study targets only African-American women.

Is there other work planned or being done on Hispanics and Native American women in this area, or some other reason not to include them in this study?

And secondly, the fourth project is called Recruitment and Retention of African–Americans in Clinical Studies. Is this not a problem with Hispanics, Native Americans and other minorities? Is there other work planned or being done in this area with them, or are there other reasons such as language or cultural factors not to include them in this particular project?

Dr. VARMUS. Well, I certainly can look into those specific projects for you for the record. As you know, in the course of the last year, we have developed guidelines for inclusion of minorities and women in all clinical research projects at NIH. And it would be incumbent upon any investigator who is proposing a study of clinical problems of the type you are describing to explain to NIH why there would be the exclusion of certain groups that might be at risk for the disease in question.

Thus, our clinical investigators are obliged to now explain to NIH staff and to study section reviewers if they have incorporated any restrictions in their grant proposals based on race, gender or ethnicity.

[The information follows:]

HIGH RATES OF DIABETES IN MINORITY POPULATIONS

NIDDK, concerned by the high rates of diabetes and obesity in minority populations, has developed research programs to address these critical health areas.

To address the prevalence of diabetes mellitus among minorities, NIDDK recently funded applications received in response to two requests for applications (RFAs) entitled "Clinical Intervention Studies in Diabetes Mellitus Among Native Americans and Alaska Natives" and "Intervention Studies in Diabetes Among Minority Populations". Both RFAs were specifically designed to develop and validate intervention approaches for the amelioration or prevention of diabetes mellitus and/or its complications among minority populations. These research grants were awarded according to scientific merit as determined by the NIH peer review system and were selected to provide information on the minority population at high risk. Thus, studies are presently being conducted in several Native American tribes, Alaskan Natives, African-Americans, Hispanics, Native Hawaiians, and Asian Americans. We expect that these investigators will meet jointly to discuss their progress and approaches that may be amenable to their particular study population.

Since obesity is a condition that affects minority populations disproportionately, particularly minority women, NIDDK has undertaken a major obesity initiative to emphasize its commitment to the area of nutrition and obesity. Obesity/Nutrition Research Centers (ONRC) and a National Task Force on Prevention and Treatment of Obesity have been established to strengthen multidisciplinary research in obesity and nutrition in biomedical research institutions. Further, in 1993, NIDDK sponsored an international workshop on "Prevention of Obesity: Populations at Risk, Etiologic Factors, and Interventional Strategies". The central objective of the workshop was to identify specific recommendations for future research with specific emphasis on the health implications for women and minority populations.

With respect to the recruitment and retention of African-Americans in clinical studies, NIDDK has designed the study in conjunction with a currently ongoing clinical trial that addresses the need to examine the high prevalence of hypertension and hypertensive kidney disease in African-Americans. Studies show that, compared to whites, African-Americans are five times more likely to contract hypertensive kidney disease. Further, clinical studies have shown that African-Americans react differently to blood pressure medications. Thus, current therapies for treatment of high blood pressure are not completely effective in African-Americans. Other minority populations were not excluded from this project for reasons other than the fact that the project uses participants in an existing clinical trial. Such a project design could be developed in conjunction with clinical trials associated with other minority populations.

Mr. SERRANO. Mr. Chairman, I am going to forgo the rest of my questions, since I know there is very little time. But I just wanted to say, Doctor, that my questions should be taken for what they are. They reflect concerns of a group of legislators who are joined by many others about the work being done by an agency that we support very strongly and that we will continue to support. So don't take these questions as a lack of support. We support you. We want you to continue to grow in any sense. We will do whatever we can to help you.

In the meantime, we want you to pay close attention to the fact that there is a population that sometimes is not included in the research and in the work, and while we support you, we also want you to take care of that also.

Dr. VARMUS. Thank you, I appreciate your concerns and support.

Mr. SMITH. Ms. DeLauro.

OCCUPATIONAL HEALTH ISSUES

Ms. DELAURO. Thank you very much, Mr. Chairman, and Dr. Varmus. Let me also congratulate you on your appointment to lead the NIH. As my colleagues have said, and I think you can discern from past history, this committee believes in the NIH and its mission and wants to continue to make it the premier research institution in the world. And I associate myself with the other comments that were made this morning.

There are two other areas previously discussed I would like to mention as well. One has to do with the comments of my colleague, Ms. Pelosi, in support of the Office of AIDS Research and for the consolidation of the budget there. And I also associate myself with the comments that my colleagues have made about the importance of treating women and minorities with equity at the NIH. I think that that is something about which we are all very, very concerned.

Let me ask one or two questions, if I might. Your budget justification indicates that you are requesting an additional $5.6 million for the Office of Research on Women's Health. And one of the activities that you expect to carry out is support for research into occupational health issues, including the physiological differences between men and women that make them more or less susceptible to particular hazards in the workplace.

I applaud this look at occupational exposure to health hazards, because I think that research in the past has not looked at the hazards that may particularly affect women in the workplace and because women, particularly those of childbearing age, have been excluded from certain jobs on the basis of presumed reproductive health risks.

Can you tell me what type of research in this area is already under way and what new initiatives are anticipated?

Dr. VARMUS. I don't know the specific projects that are to be undertaken in that area, Ms. DeLauro. I will be happy to provide them for the record.

[The information follows:]

GENDER DIFFERENCES AND OCCUPATIONAL HEALTH RISKS

Hazards for women in the workplace have been recognized for over 100 years. Among the institutes at the NIH, the National Institute of Child Health and Human Development (NICHD), National Cancer Institute (NCI), and the National Institute of Environmental Health Sciences (NIEHS) are actively assessing potential gender differences in health risks from occupational exposures.

One particularly modern, potential hazard is the video display terminal. The NICHD is currently supporting a study examining early pregnancy loss among female office workers, specifically looking at the use of video display terminals as a risk factor. Although epidemiological studies carried out in this country, as well as overseas, have not found an association, they did not measure the actual exposure of workers to electromagnetic radiation. Because these emissions vary with different terminals, which do not all emit radiation above the amount normally found in the atmosphere, we need to determine safety levels for pregnant women. Currently, investigators are analyzing data on more than 4,000 subjects.

In another NICHD-supported study, investigators are addressing the epidemiology of pregnancy in a textile community. This study grew out of a concern that female textile workers may be at an increased risk of adverse reproductive events. Currently, investigators are editing the extremely complex data that were collected.

For the future, several critical issues must be addressed. One is to assess the effect of environmental insults upon maternal gametes (oocytes). The complement of available oocytes is established in early development and any damage that is incurred accompanies the woman for life. The observation that in developed countries between 1940 and the present the average sperm count has decreased by 50 percent adds some urgency to the need to determine if oocytes have been similarly affected.

In addition to concerns regarding fertility/infertility, other questions need to be answered concerning the effects of workplace environment on early embryonic development, fetal development, pregnancy, and delivery.

The NCI, along with the NIH Office of Research on Women's Health, the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health, sponsored a recent conference on "Women's Health: Occupation and Cancer." The conference brought together investigators from around the world to describe their work related to gender differences in cancer risk and to identify promising areas of future research. The conference proceedings will appear in the *Journal of Occupational Medicine* later this year.

NCI has a number of recently completed studies including ones in the field which will allow comparison of cancer risks from occupational exposures among men and women. The Case-Control Studies of Lymphatic and Hematopoietic Cancer in Nebraska was recently completed. This work focused on agricultural exposures, including pesticides. Women who are involved in treating livestock with pesticides have risks of non-Hodgkin's lymphoma and multiple myeloma that are higher than those observed among men. It is unclear, however, whether these higher risks represent differences in level of exposure, special susceptibility, or other factors, or simply occurred by chance.

In the mortality among aircraft maintenance workers study, a cohort mortality study of civilian workers at Hill Air Force Base in Utah, excesses of non-Hodgkin's lymphoma and multiple myeloma were associated with potential exposure to organic solvents. Relative risks tended to be higher among women than men, but the numbers were small.

In a study of cancer risks by occupation based on death certificates from 24 states, white men and women listed as farmers on death certificates had elevated risks of leukemia, non-Hodgkin's lymphoma and multiple myeloma. Male and female teachers tended to experience elevated mortality from multiple myeloma and non-Hodgkin's lymphoma. Soft tissue sarcoma was elevated among women employed in the telephone industry and breast cancer was associated with possible occupational contact with solvents and metals.

No strong differences in risk by job title or occupational exposure were noted between men and women in a study of occupational exposures and multiple myeloma among men and women in Denmark.

In a study of cancer mortality among furniture workers, an extended update of a cohort of the furniture workers found a nonsignificant excess of cancer of the buccal cavity and pharynx among black and white women, but not among men. Both men and women experienced small excesses of cancers of the stomach and pancreas.

A cohort study of approximately 40,000 women and 40,000 men exposed to benzene in China noted elevated risks for leukemia and non-Hodgkin's lymphoma in both sexes. Men, however, experienced an excess of lung cancer, whereas women did not.

A study of cancer mortality among jewelry workers showed that mortality from cancers of the esophagus, colon, and lymphatic and hematopoietic system was elevated among both men and women engaged in the manufacture of jewelry. Women experienced an excess of stomach cancer and multiple myeloma, while men did not.

The occupational mortality among women in a study of 15,000 cancer deaths among women in Russia noted many occupational associations previously observed among men, including stomach and lung cancers among miners, lung cancer among drivers, and leukemia among physicians and scientists.

In the mesothelioma and asbestos exposure study, occupational exposure to asbestos substantially increased the risk of mesothelioma among men and women.

There are also several ongoing investigations examining gender differences in occupational settings. The Agricultural Health Study is a long-term prospective study of men and women in Iowa and North Carolina and is designed to evaluate agricultural factors that may contribute to the development of cancer and other chronic diseases and reproductive outcomes. Information on agricultural exposures and lifestyle factors is being obtained from farmers and their spouses and commercial pesticide applicators. The cohort is expected to include over 30,000 women. Enrollment of cohort participants started in December, 1993 and will continue through 1996.

In a mortality study of dry cleaners, the follow-up of approximately 5,000 dry cleaners is being extended to include an not only those deaths prior to 1980 but an evaluation of the deaths from 1980 up to 1994. The cohort includes about 2,500 white women, 1,500 black women, 400 white men, and 900 black men employed in the dry cleaning industry who may have had exposure to dry cleaning solvents. An earlier evaluation of this cohort noted slight excesses of cancer of the bladder and lymphatic system, but with no substantial differences between men and women.

In the case-control studies of cancers of the brain and stomach, studies of these tumors are being conducted among men and women in Nebraska to evaluate agricultural exposures. Both cancers have been found to be elevated among farmers in many countries, but the specific factors that may be involved have not been identified.

The mortality experience of Hill Air Force Base employees is being extended from 1981 through 1994 to further evaluate the association observed in the earlier study between non-Hodgkin's lymphoma and multiple myeloma and organic solvents, particularly among women.

In the extended follow-up of formaldehyde workers the mortality experience of men and women exposed to formaldehyde is being extended from 1980 through 1994 to evaluate cancer risks that may be associated with exposure to this chemical.

Acrylonitrile, a major chemical used in the manufacture of plastics, is carcinogenic in animals. A mortality study of workers at eight facilities using or producing this chemical will be completed in 1996. This cohort includes about 5,500 women.

Well-established occupational hazards such as asbestos, chromium, benzene, arsenic, nickel, radon, benzidine, and wood and leather dusts will continue to exert their untoward health effects, even though recent control of exposures should diminish their impact in the future. Because of gender specific employment patterns in the past, men have had the predominant exposures to these substances.

Occupational exposures of concern today include pesticides, solvents, exotic metals, combustion products, and electromagnetic radiation. The evidence for the human carcinogenicity of these substances is not clear. However, these exposures are of concern to both women and men, because they can be found in occupational and non-occupational settings.

The NIEHS supports studies on occupational exposures as part of its mission to investigate the environmental causes of disease and dysfunction. Ongoing research includes epidemiologic studies of reproductive function in semiconductor workers exposed to a variety of solvents and metals, the pulmonary effects of exposure to grain dusts in farmworkers, and a study investigating the effects of exposure to mercury and nitrous oxide in dental hygienists.

Ms. DeLauro. Further on that, I would very much like to see the goal of the new research, as identifying risks to women, and is its purpose to identify those risks and to demonstrate as well how one might eliminate those risks.

Dr. Varmus. Yes, certainly. That is the principle, but specifics, I don't know.

INCLUSION OF WOMEN AND MINORITIES IN TRIALS

Ms. DeLauro. Also, your budget justification indicates that the Office of Research on Women's Health and the Office of the Director are preparing and will disseminate the NIH notebook on inclusion of women and minorities in clinical research. The notebook is anticipated to serve as a primer for scientists in how to recruit and retain women in clinical studies.

When will the notebook be released?

Dr. Varmus. The guidelines, of course, have been published. The notebook, Dr. Baldwin tells me, will be available very soon, which I assume means the next two months, within two months.

Ms. DeLauro. Within two months? Very soon has a——

Dr. Varmus. I know. I want to be more explicit. We will try to provide you with it by the first of July.

Ms. DeLauro. Thank you. Will this be the primary tool that you will use to educate researchers as to the requirement that women be included in clinical trials, as well as a how-to manual?

Dr. Varmus. It will be a tool, but we expect investigators who have difficulty in complying with the guidelines or fail to understand them, to call us and to interact directly with Dr. Baldwin's office and administrators in the Institute to which they are making grant applications.

So we understand that there may be difficulties, especially with attempts to recruit not simply Hispanics but components of different Hispanic communities, and that we may need to assist investigators in making collaborative arrangements with people in other parts of the country to conform with the guidelines that we published.

Ms. DeLauro. And there will be a—rather than just responding to inquiries in this effort, there will be a proactive——

Dr. Varmus. Absolutely.

Ms. DeLauro [continuing]. Effort to move out to talk to people in this area?

Dr. Varmus. We are very responsive to the concerns in the clinical community that these guidelines could make life difficult for a clinical investigator. We want to show them there are ways they can do the research they intend to do in a way that is equitable and meets the guidelines and without encumbering their research efforts.

TOPICAL MICROBICIDES

Ms. DeLauro. Okay. I am very happy to see that the budget request includes additional support for HIV/AIDS-related research. The budget justification indicates that $10 million of the increased funds requested will be focused exclusively on research to develop safe, effective microbicides designed for use by women to prevent sexually transmitted infections, including HIV infection and other sexually transmitted diseases.

I happen to believe, and my colleague Connie Morella has done a lot of work in this area, that this is really critical, that women must have a method to prevent the spread of STD and the HIV virus that they themselves can control.

How much has the NIH spent so far researching microbicides designed for use by women?

Dr. VARMUS. About $12 million so far.

Ms. DELAURO. About 12?

Dr. VARMUS. $12 million.

Ms. DELAURO. Has a lack of funding prohibited a more intensive effort to date in this area?

Dr. VARMUS. This area is projected to more than double in funding between FY 1994 and FY 1995, increasing from $12 million to $25 million.

Ms. DELAURO. Thank you. Which Institute will carry out the research utilizing the $10 million in additional funds that have been requested?

Dr. VARMUS. It will principally be two institutes, the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Child Health and Human Development (NICHD).

Ms. DELAURO. And I will have the opportunity to talk more about that with you later, Dr. Fauci, and others in the ensuing days. But, again, I just want to say for the record that this is extremely important research and I would hope that the NIH would move very quickly into developing very safe and effective and easy use products for women. I think that this is one of the primary ways in which we can begin to get some control of the AIDS crisis.

Thank you very, very much, Dr. Varmus. I look forward to working with you in the months ahead.

Thank you, Mr. Chairman.

FTE INCREASES IN ICDS

Mr. SMITH. I notice that Mr. Hoyer was talking about the number of FTEs. There has been an increase in the number of FTEs in the last 10 years in all Institutes but two. One of them was NIDDK. There has been a 19 percent reduction in the number of FTEs there, and in nursing research, a whopping 43 percent reduction.

What is the reason for this? Why are those two Institutes allocated fewer FTEs and all the rest of them more?

Dr. VARMUS. We think that is a ten-year comparison.

Mr. SMITH. It is a ten-year comparison?

Dr. VARMUS. Yes, the difficulty there is, of course, the Institute was divided.

Mr. SMITH. Which Institute is divided?

Dr. VARMUS. Well, it would have been the Arthritis and Metabolic Disease Institute that was divided into two Institutes, the National Institute of Arthritis and Musculoskeletal Disease (NIAMS) and NIDDK.

Mr. SMITH. What accounts for the nursing research?

Dr. VARMUS. Since its inception in 1986, the National Institute for Nursing Research (NINR) has experienced a steady increase in FTEs. It appears that the numbers of FTEs were transposed between NINR and NCRR in the material provided to the committee in preparation for the hearings.

Mr. SMITH. It is not a new institute.

Dr. VARMUS. It is nine years old. It previously was the National Center for Nursing Research. It was established in 1986.

Mr. SMITH. Okay. Well, will you look into that and explain it in the record? I become suspicious, though, because all the way, it seems like, in the process of developing budgets over the years, nurses get dropped through the cracks. If there is an alternative between one thing, doctors or nurses or whatever it is, it seems like nurses come out second best usually. I became suspicious when I looked at those statistics there.

Mr. Porter.

Dr. VARMUS. I am sure Dr. Hinshaw was happy to hear that.

[The corrected information follows:]

CORRECTION OF FTE HISTORY TABLE

The 10-year Full-time Equivalent (FTE) history table appearing on page 53 of the document entitled "National Institutes of Health: Key Facts and History of Funding, FY 1984–FY 1994" contains inaccurate information for the National Institute of Nursing Research and the National Center for Research Resources for the years 1984–1992. NINR actually experienced growth from 5 FTEs in FY 1986, the first year of their existence, to 52 FTEs in FY 1994, more than a ten-fold increase. Concurrently the National Center for Research Resources gained 13 FTEs over the past 10 years, a 12 percent increase. The attached table correctly depicts the data for these two NIH components.

NATIONAL INSTITUTES OF HEALTH
Full-Time Equivalents (FTEs)

ICDs	FY 1984	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Appropriation
NCI	2,416	2,230	2,101	2,110	2,283	2,173	2,192	2,345	2,525	2,601	2,400
NHLBI	863	847	806	833	865	842	845	881	912	911	885
NIDR	335	328	329	337	344	335	327	330	352	362	362
NIDDK	716	674	582	595	610	597	599	603	629	638	660
NINDS	694	666	658	688	693	652	662	721	723	709	716
NIAID	745	737	702	732	806	870	919	1,005	1,091	1,136	1,144
NIGMS	169	161	157	156	153	158	172	183	190	191	188
NICHD	462	433	421	428	437	438	448	502	550	562	523
NEI	234	215	198	196	217	212	213	229	260	272	257
NIEHS	695	670	665	682	689	667	667	701	721	750	735
NIA	378	356	341	346	356	356	365	402	439	472	458
NIAMS	0	0	49	67	104	113	118	138	162	166	150
NIDCD	0	0	0	0	0	37	58	97	122	133	117
NIMH	889	855	779	819	869	861	868	903	934	948	957
NIDA	270	241	193	205	260	282	313	356	400	424	401
NIAAA	212	196	198	193	194	213	227	232	241	254	244
NINR	0	0	5	15	26	31	28	38	46	52	52
NCRR	91	91	86	89	97	94	90	98	104	108	102
NCHGR	0	0	0	0	0	0	26	37	44	55	153
FIC	61	60	56	56	58	58	59	67	72	75	80
NLM	544	531	501	510	510	511	550	585	602	625	614
OD	587	567	506	504	514	586	626	685	699	716	717
Cen. Svcs.	4,671	4,534	4,377	4,376	4,487	4,502	4,571	4,734	4,951	4,945	4,889
Total	15,032	14,392	13,710	13,937	14,572	14,588	14,943	15,872	16,769	* 17,105	* 16,804

* Formerly ceiling-exempt FTE utilization is included in FY 1993 and FY 1994.

Average Cost of an FTE
(Dollars in Thousands)

	FY 1984	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993	FY 1994 Appropriation
NIH	$34.1	$35.7	$37.3	$38.9	$40.7	$42.5	$46.8	$48.9	$51.2	$56.5	$60.6

CRIMINAL PENALTIES FOR SCIENTIFIC FRAUD

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Varmus, I apologize for having to leave. My two subcommittees meet in adjoining rooms, so I sort of run back and forth between the two of them. And I, unfortunately, missed the discussion about the falsification of research that you had, I understand, with Mr. Bonilla.

Let me just ask one question that I don't think he asked, and that is: Should we have in our law criminal penalties for the intentional falsification or fabrication of research data? In other words, is there enough deterrence in just not being funded or shouldn't we have the threat of actually paying a price to society for providing known intentionally fabricated or false data?

Dr. VARMUS. I personally have no objection to criminal penalties. It would be a useful way to advertise the clear nature of behavior which is fundamentally criminal in intent, in which money provided by the Federal Government, or other agencies for that matter, is abused by activities that I consider to be criminal.

Mr. PORTER. I think the public, certainly myself, I think people were shocked by this. Unfortunately, the nature of news is always negative. The public out there doesn't hear all the wonderful things NIH does. It hears these kinds of things and they kind of blare out in the newspaper headlines or on your television screen and destroy a reputation built for a long, long time. Suddenly people say, "Oh, we don't have any faith anymore because, obviously, there are people doing this."

Now, it is impossible in the overall sense if someone is intent upon doing something criminal to prevent it, but it seems to me to provide strong deterrence so the people won't do it, is a very good thing to do, and criminal penalties might be a further deterrence to just defunding.

Dr. VARMUS. It seems to me that effective deterrents may exist already. It is just a question of whether they are being pursued.

FY 1995 INCREASE IN RPGS

Mr. PORTER. I don't think they do, actually. But we are looking into it and we are going to see. Let me ask, and you and I have discussed this, but I want to get your answer on the record. You are requesting funding for 7,292 new and competing grants this year. That is well above the recent historic average of about 6,000 new grants per year. It appears to require substantial outyear investment. However, the total number of grants would actually decline from 24,010 to 23,890.

Why are you requesting this large number of new grants and what will be the out year impact on NIH's budget in the total number of grants?

Dr. VARMUS. Well, the reason for the seemingly large number of new and competing grants in the coming year is the reflection of the decreased length of the grants that resulted, in part, from congressional advice some years ago, in 1989 and 1990. The average length of awards was decreased.

A consequence of this reduction was the substantial increase in the number of investigators applying for competitive renewals of grants awarded in 1990, in the coming year. Thus, there are more new and competitive awards this year. We don't expect this to happen in the following year.

Mr. PORTER. So this would be a blip, rather than long term?

Dr. VARMUS. It will be a blip in the chart rather than a series of incremental increases in our commitment base.

Mr. PORTER. I am concerned about earmarking, as I mentioned, in the NIH budget, both by Congress and by the administration. And I would like to know if you can tell us what changes in priority were made in your budget from the time it first left NIH for departmental and OMB review and the time it was formally submitted to Congress?

Dr. VARMUS. We can provide a chart that shows all that for the record if you like. You will see there are very few changes over the course that have occurred throughout the development of the NIH budget.

Mr. PORTER. They may be few in number, but they may be big in implication. I would like to see that. If you could provide it.

Dr. VARMUS. Yes, you are welcome to it.

Mr. PORTER. I would very much like to see it.

[The information follows:]

DHHS–NATIONAL INSTITUTES OF HEALTH

CHRONOLOGY OF 1995 PRESIDENT'S BUDGET
(Dollars in Thousands)

	1994 APPROPRIATION			PHS ESTIMATE TO DHHS 1/			DHHS ESTIMATE TO OMB		
	Non–AIDS	AIDS	TOTAL	Non–AIDS	AIDS	TOTAL	Non–AIDS	AIDS	TOTAL
NCI	$1,868,810	$213,457	$2,082,267				$1,979,298	$223,919	$2,203,217
NHLBI	1,222,903	54,977	1,277,880				1,259,810	58,292	1,318,102
NIDR	158,089	11,431	169,520				162,676	12,184	174,860
NIDDK	705,616	10,438	716,054				727,510	11,126	738,636
NINDS	608,545	22,105	630,650				627,051	23,446	650,497
NIAID	520,792	544,791	1,065,583				540,901	577,298	1,118,199
NIGMS	851,566	23,945	875,511				879,464	25,600	905,064
NICHD	498,769	56,426	555,195				513,560	60,144	573,704
NEI	281,879	8,381	290,260				290,456	8,934	299,390
NIEHS	258,641	5,608	264,249				267,127	5,942	273,069
NIA	418,639	1,664	420,303				431,815	1,731	433,546
NIAMS	220,485	2,795	223,280				227,332	2,979	230,311
NIDCD	161,316	1,507	162,823				166,396	1,567	167,963
NIMH	526,262	87,182	613,444				539,336	93,424	632,760
NIDA	281,825	143,376	425,201				288,662	152,823	441,485
NIAAA	176,160	9,457	185,617				181,391	10,071	191,462
NINR	46,574	4,444	51,018				48,556	4,736	53,292
NCRR	270,532	61,383	331,915				283,340	65,427	348,767
NCHGR	128,701	---	128,701				150,757	---	150,757
FIC	12,825	8,852	21,677				13,581	9,423	23,004
Subtotal	9,218,929	1,272,219	10,491,148				9,579,019	1,349,066	10,928,085
NLM	116,899	3,082	119,981				133,850	3,205	137,055
OD	207,861	25,744	233,605				235,100	26,781	261,881
B&F	111,039	---	111,039				118,731	---	118,731
Total, NIH	9,654,728	1,301,045	10,955,773	$9,824,984	$1,385,000	$11,209,984	10,066,700	1,379,052	11,445,752

1/ Estimates submitted in total, information not available by ICD.

DHHS–NATIONAL INSTITUTES OF HEALTH

CHRONOLOGY OF 1995 PRESIDENT'S BUDGET
(Dollars in Thousands)

	PRESIDENT'S BUDGET			PROFESSIONAL JUDGMENT		
	Non–AIDS	AIDS	TOTAL	Non–AIDS	AIDS	TOTAL
NCI	$1,967,709	$222,712	$2,190,421	$3,346,059	$253,941	$3,600,000
NHLBI	1,266,961	57,910	1,324,871	1,725,827	71,776	1,797,603
NIDR	163,776	12,097	175,873	259,304	19,696	279,000
NIDDK	731,500	11,047	742,547	868,835	13,048	881,883
NINDS	630,443	23,291	653,734	906,348	31,623	937,971
NIAID	542,864	578,109	1,120,973	755,148	789,947	1,545,095
NIGMS	882,189	25,409	907,598	1,063,789	28,457	1,092,246
NICHD	516,736	64,155	580,891	666,775	108,505	775,280
NEI	292,022	8,870	300,892	359,584	15,494	375,078
NIEHS	267,955	5,903	273,858	350,477	8,191	358,668
NIA	433,701	1,723	435,424	571,777	2,311	574,088
NIAMS	228,413	2,958	231,371	320,430	3,991	324,421
NIDCD	167,129	1,560	168,689	250,460	2,720	253,180
NIMH	545,223	92,704	637,927	649,110	117,696	766,806
NIDA	291,963	151,733	443,696	441,891	174,609	616,500
NIAAA	182,498	10,000	192,498	214,329	10,346	224,675
NINR	48,326	4,702	53,028	61,595	13,239	74,834
NCRR	286,394	64,960	351,354	386,186	83,291	469,477
NCHGR	152,010	– – –	152,010	213,267	– – –	213,267
FIC	13,745	9,357	23,102	38,500	12,639	51,139
Subtotal	9,611,557	1,349,200	10,960,757	13,449,691	1,761,520	15,211,211
NLM	135,330	3,191	138,521	284,538	3,205	287,743
OD	233,522	26,661	260,183	310,467	77,888	388,355
B&F	113,539	– – –	113,539	702,383	– – –	702,383
Total, NIH	$10,093,948	$1,379,052	$11,473,000	$14,747,079	$1,842,613	$16,589,692

AIDS FUNDING OPTIONS

Mr. PORTER. Could I ask a question of Mr. Mahoney about the other options that NIH and the Department considered in regarding the AIDS line? What were those other options and were they consistent with the statute?

Mr. MAHONEY. Mr. Porter, One other option was to identify in ICD bill language the precise amount for AIDS and provide the OAR Director with transfer authority. Another option that was considered was to provide separate appropriations similar to the FY 1994 budget with no specific AIDS earmarking, but with transfer authority.

As Dr. Varmus has said, we decided in our discussions, and the Secretary agreed, that the display that is presented to you in the President's budget follows most closely what we perceive to be the intent of the authorizing legislation.

Mr. PORTER. Well, I am still very much concerned about ceding our subcommittee's authority, delegating funding. And, Dr. Varmus, wouldn't we be better served to appropriate the funding by Institute as we always have done, cognizant of the AIDS plan developed by Dr. Paul's office, and then permit changes midstream if they are needed through the regular reprogramming process?

Couldn't we do it that way and rather than to put all of this in one line item?

Dr. VARMUS. I think you could argue, Mr. Porter, that that would give the Director of the Office yet more authority, because you would then allocate to the Institutes and give him transfer authority throughout the year.

As it stands, the AIDS budget is broken down by Institute. The Director of OAR is directed to distribute that money to the Institutes within 15 or 30 days depending on the purpose of the money. Then there is, of course, a one percent transfer authority issued to the Director of OAR to allow for support of high priority research and public health emergencies with respect to AIDS.

Mr. PORTER. I disagree. I think it would leave control in the subcommittee on the reprogramming side. I am concerned about having that single earmark in the budget as a single line item.

Well, thank you very much for being here today, for testifying, for answering all of our questions. I have to say, I am very impressed at how quickly you have gotten a grasp of all this, including all of the detail of NIH. It is rather amazing.

Thank you very much, Dr. Varmus.

Mr. SMITH. Thank you very much, Doctor. And I, too, hope that next year is a good year. Thank you.

We will be back at 2:00.

[The following questions were submitted to be answered for the record:]

RECOMMENDATIONS OF THE INTRAMURAL REVIEW PANEL

Mr. Smith: We understand that the report on the intramural program produced by Dr. Marx and Dr. Cassell's outside panel is now complete. Since the draft report has been just delivered to us, can you summarize its main points for us?

Dr. Varmus: In its Executive Summary, the Report of the External Advisory Subcommitte (EASC) of the Director's Advisory Committee, National Institutes of Health recommends: 1) The establishment of a standing Advisory Committee to the Deputy Director for Intramural Research consisting of the chairs of each of the Institutes' Boards of Scientific Counselors to provide ongoing review of intramural quality control processes; 2) Improved selection of members for the Boards of Scientific Counselors and more rigorous criteria for review of NIH's Scientific Directors; 3) Centralization of review of candidates for tenure; 4) Greater emphasis on independence and career development for trainees at NIH; 5) Tighter linkage between NIH-funded extramural training programs for scientists from groups under-represented at the NIH and recruitment to various intramural research programs; 6) Annual institute-by-institute planning, including assessment of optimal relative allocation to extramural and intramural programs; 7) Streamlining of procurement and travel procedures; 8) Broad annunciation of our policies and purposes served through Cooperative Research and Development Agreements; 9) Phased renewal of Clinical Center facilities, starting with a 250-bed hospital funded by additional allocations from Congress; 10) Prioritization and consolidation of use of space; and 11) Re-classification of the Intramural Research Program as a non-administrative expense.

Mr. Smith: How do you plan to respond to the report? Do you disagree with any of its conclusions?

Dr. Varmus: We are currently drafting our response to the report. We are largely in agreement with its recommendations, and have already begun to implement some of them, such as improvements in the tenuring system; formation of a NIH-wide Tenure Committee; tightened linkages between extramural training and intramural recruitment programs to attract under-represented scientists; planning of a "Reinventing Government" model program to streamline procurement, travel and other administrative functions; and improvement in intramural review through the Boards of Scientific Counselors.

Mr. Smith: How do these recommendations affect your plans for the construction of a new Clinical Center?

Dr. Varmus: The EAC report has given us valuable suggestions on appropriate sizing of a new research hospital for the Clinical Center and how such a facility should be funded. The first phase of the renewal of the Clinical Center--a new hospital with essential laboratory facilities--will be much less costly than a total replacement facility.

Mr. Smith: What are the budgetary implications for the intramural program in general and for the Clinical Center in particular?

Dr. Varmus: The EAC report also recommends that the intramural program not grow disproportionately relative to the extramural program, and that funding of the new Clinical Center facilities should not adversely impact either extramural or quality intramural research programs.

RECRUITMENT AND RETENTION OF INTRAMURAL SCIENTISTS

Mr. Smith: What ideas do you have for recruiting and retaining top talent for the intramural program?

Dr. Varmus: At present, our ability to recruit and retain top talent in the intramural program is impaired by a PHS-wide hiring freeze and prohibition on promotions to the GS-14 level or above--a typical job classification for some of our most productive, newly-tenured young scientists. We are also pursuing SBRS and Title 38 authorities to recruit outstanding senior talent to NIH. This authority, combined with an end to the employment freezes mandated by PHS, and broadened searches recommended by the External Advisory Committee, should help us bring some exciting new investigators to NIH.

CONSTRUCTION OF CLINCIAL CENTER COMPLEX

Mr. Smith: Do you expect to begin requesting funding for Clinical Center construction in the 1996 budget?

Dr. Varmus: Funding for the planning and design of the Clinical Center (CC) project could be requested in FY 1996. The decision to request funds will depend on: (1) the recommendations of the External Advisory Committee review of the NIH Intramural Research Program; (2) the relative priority of the Clinical Center renewal compared to other NIH/HHS, and government-wide priorities, as determined by the NIH Director, the Assistant Secretary for Health, the Secretary of HHS, and the President. Currently, the FY 1995 budget includes $2.5 million to develop options relative to the replacement or restoration of the existing facility.

TRANS-INSTITUTE FOCUS OF INTRAMURAL PROGRAM

Mr. Smith: There were reports earlier this year that you wanted to proceed with creating trans-Institute faculties in the NIH intramural program and with establishing an NIH graduate school. Are these plans underway, and do they require any funding in 1995?

Dr. Varmus: In accordance with the EAC recommendations, we are not currently pursuing plans for a graduate school. We have encouraged NIH intramural scientists to pool their expertise and improve communication through Inter-Institute Interest Groups, a grass-roots organizing effort that has resulted in six major groups: Neurobiology, Genetics, Structural Biology, Molecular Biology, Cell Biology, and Immunology. In addition, several smaller, more focused interest groups are springing up. This year I have offered these groups $60,000 from my Discretionary Fund to help cover the expenses of outside speakers invited to campus to present topics of broad interest to NIH scientists.

THE WOMEN'S HEALTH INITIATIVE

Mr. Smith: The IOM report criticized the cost estimates for the Women's Health Initiative, saying that it was likely to cost substantially more than the $625 million estimated. Do you think the costs of the study are understated?

Dr. Varmus: The current cost estimates for the Women's Health Initiative are realistic, conservative and not understated. Considerable care went into development of the estimates by NIH staff and we now have an independent estimate of costs and the initial experience in the actual contracting according to these estimates. The independent estimate made by Dr. Nicole Urban, an economist at the Fred Hutchinson Cancer Research Center, agrees closely with Government estimates. There is experience in writing contracts for the coordinating center and the first 16 clinical centers awarded. These contracts are very close to Government estimates. The centers have been performing contract work for slightly more than a year and are within budget. Contracts are being negotiated for the next 29 clinical centers.

Mr. Smith: Dr. Varmus, if you had been the head of NIH when the Women's Health Initiative was originally conceived, would you have recommended that the project go forward? Is this the best way to spend $625 million on women's health?

Dr. Varmus: It is not appropriate for me to comment on an action taken by another NIH Director 4 years ago when the context was different than today. I have reviewed the program and its progress. The issues being addressed by the Women's Health Initiative were then and remain today extraordinarily important to women's health and can only be answered by large, well planned studies. Hormonal replacement therapy and nutrition play important roles in preventing heart disease, cancer, and osteoporosis. These conditions are responsible for much of the death, disability and impaired quality of life among older women. The program addresses these issues. I have reviewed the program and the assessment by the Institute of Medicine with consultative advice from outside scientists. I have decided that the program should continue as planned and is an effective investment in women's health. I have agreed, however, to reassess these studies at the end of 6 years and make a determination regarding their continuation.

AIDS RESEARCH

Mr. Smith: There have been reports of congressional interest in funding a Manhattan Project-style effort for AIDS research. What do you think of this proposal?

Dr. Varmus: Virtually every Institute, Center and Division of the NIH conducts and supports HIV/AIDS research, coordinated by the newly-strengthened Office of AIDS Research. With the enactment of the NIH Revitalization Act of 1993, the Office of AIDS Research has the responsibility to develop an annual trans-NIH AIDS research plan, based on the current scientific opportunities and priorities. This research plan is developed by scientific experts at the NIH, HIV and non-HIV expert researchers outside the NIH, as well as community representatives, reflecting the best considered approach to HIV research. Thus, the NIH AIDS research program could be compared in many ways to a Manhattan Project approach to biomedical research.

However, whereas the physical scientists in the Manhattan Project had the basic scientific information necessary to build an atomic bomb, the biomedical and behavioral scientists still lack sufficient basic scientific knowledge to prevent HIV transmission or to cure AIDS.

Another interpretation of a Manhattan Project-style effort is a highly focused endeavor to comprehensively obtain more information in a particular area of science. The NIH AIDS planning process and the work of the OAR Coordinating Committees are designed to delineate specific scientific questions which are an impediment to scientific advancement. Thus, the OAR, with its Discretionary Fund and its use of experts from across the NIH and the country, can identify scientific impediments and initiate focused research initiatives to answer specific questions.

Mr. Smith: Does the Office of AIDS Research plan to substantially revise the current AIDS plan in 1994?

Dr. Varmus: As mandated by the NIH Reauthorization Act of 1993, the NIH Plan for HIV-Related Research will be updated annually. The Office of AIDS Research has recently completed its planning process for FY 1996 which will serve as the framework for the FY 1996 NIH AIDS budget submission. This planning process will serve as a model for the future to seek advice and input from experts from the intramural and extramural NIH community, outside experts in AIDS and related fields, and community representatives.

The planning process for FY 1996 began with the establishment of the five OAR Coordinating Committees in each of the areas of emphasis of HIV-related Research: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral Research. These committees comprise representatives from the NIH institutes with the largest research investment in that area. The Coordinating Committees reviewed the FY 1995 NIH Plan for HIV-Related Research, updating and revising the plan to reflect current scientific opportunities and priorities. That document was then reviewed by the

Directors and AIDS Coordinators of each of the NIH Institutes, Centers and Divisions.

A large workshop of 150 experts was then convened, including the members of the Coordinating Committees, as well as researchers and scientists from academia, industry, and government and community representatives. Five concurrent workshops for each of the areas of emphasis worked over three days to refine, revise, and reach consensus on the objectives, strategies, and priorities for NIH research in FY 1996 within each area.

Finally, a small group of eminent scientists was convened to review the plan, and to determine the overall major scientific priorities for the NIH. The Deputy Director of NIH and I also participated in this meeting. Thus, the FY 1996 NIH Plan for HIV-Related Research represents a consensus not only of scientists and the leadership of NIH, but experts and scientists around the country, and representatives of the community. The plan reflects serious deliberation and discussion of experts, both in light of scientific opportunities and disappointments, as well as financial constraints.

THE FUTURE OF RESEARCH TRAINING AT NIH

Mr. Smith: We understand that the National Academy of Sciences will soon release a report on future research training needs. Can you give us some idea of what the report will say?~

Dr. Varmus: The executive summary of the tenth National Academy of Sciences (NAS) report on National Needs for Biomedical and Behavioral Research was released on April 19. The Committee on Research Personnel Needs remains very supportive of the National Research Service Awards (NRSA) and states that

"...although the NRSA program may be relatively small as regards total numbers of trainees (less than 15 percent of the total number of graduate students training in the biomedical and behavioral sciences are supported by NRSA funds in any year), it is enormously powerful in its ability to change research emphases and to attract the highest quality individuals to research careers."

The Committee makes the following recommendations:

Raise the real value of stipends to more competitive levels: approximately $12,000 per year for predoctoral awardees and approximately $25,000 for postdoctoral awardees with less than 2 years of research experience. Maintain the real value of these stipends through annual increases of 3 percent per year.

Maintain the annual number of predoctoral awards in the basic biomedical sciences at 1993 levels, or approximately 5,175 awards, and the number of postdoctoral awards at 3,835.

Increase the annual number of NRSA awards for research training in the behavioral sciences from 1,069 to 1,450 between 1993 and 1996.

Increase the number of Medical Scientist Training Program (MSTP) awards each year from 822 in 1993 to 1,020 by 1996 and the number of postdoctoral fellows in the clinical sciences from 68 in 1993 to 160 in 1996. To achieve this expansion, we recommend that the annual number of postdoctoral trainees in the clinical sciences be decreased slightly from 2,051 to 1,805 between 1993 and 1996.

Increase the number of awards in oral health research to 430 by 1996, in nursing research to 500 by 1996, and in health services research to 360 by 1996.

Hold Minority Access to research Careers (MARC) awards constant at fiscal 1993 levels, or approximately 680 awards, pending the outcome of the present NIH evaluation study.

Examine research training opportunities for women throughout the NRSA program and strengthen the role of postdoctoral support to assist women in establishing themselves in productive careers as research scientists.

Review NIH databases as management information systems and introduce changes in data collection, analysis, and dissemination to permit more effective tracking of NRSA award recipients. Emphasis should be given to the analysis of minority participation in research and training. New funds should be directed to the evaluation of NRSA program outcomes.

Mr. Smith: Does a supply-driven model continue to make sense in research training, or should some objective number of trainees be set that balances demand for trainees with the supply coming through the pipeline?

Dr. Varmus: In this report, the NAS eschewed reliance on strict mathematical models and moved to an analysis of short-term indicators of labor market balance coupled with the use of multi-state life tables to model the supply of human resources. The Committee used expert opinion to estimate changes in future labormarket demand. This approach seems to have more face validity than previous approaches. A thorough analysis of the methodology will be available in a report to be issued in August, 1994.

FUNDS ALLOCATION AMONG NIH INSTITUTES

Mr. Smith: Dr. Varmus, over the years the Committee has used different techniques to allocate funding to the Institutes, ranging from straight percentage increases to percentiles to success rates. All these approaches have their shortcomings. What criteria should we use as we allocate funds among Institutes, without falling into the "disease of the month" trap.

Dr. Varmus: In allocating funds among the Institutes, the Committee should use the President's Budget as a guide for the distribution of funds. This budget reflects the commitment of President Clinton and Secretary Shalala to basic science, technology, and health care for the Nation's future. Additionally, the President's Budget has been developed in accordance with the policy and directives of the Director of the National Institutes of Health (NIH) with expert guidance from the NIH Institute Directors.

Of the total increase provided for NIH, funds have been set aside for special areas of increase and high priority initiatives. These high priority areas focus NIH's research effort on several specific public health issues. The remaining funds are spread equally across the Institutes to support their base research programs. It is this funding that allows the ICD Directors to use their expertise to manage their research portfolios.

INDIRECT COSTS REVIEW

Mr. Smith: The Administration has proposed a pause in indirect cost reimbursements for 1995. This approach does not address any of the underlying problems. If you had the opportunity to design a policy to "reform" indirect costs, what alternatives would you suggest?

Dr. Varmus: The Administration has proposed the pause so that the Office of Management and Budget, the Office of Science and Technology Policy, and the Council of Economic Advisors can address the underlying problems in a constructive fashion with advice from affected Federal research agencies and representative institutions. This examination will take place in 1995 while we "pause" from any other changes in policy or indirect costs reimbursements.

NIH participated in the recent revisions to OMB Circular A-21 with the OMB and other Federal research agencies. We have confidence that those revisions made some important changes that, for the most part, begin to be implemented this July and beyond as new rates are negotiated. It is expected that these changes will have a positive effect on costs and help to simplify the process. Prior to the A-21 revision process, NIH published a study of indirect costs in conjunction with the Assistant Secretary for Management and Budget and the Inspector General, HHS. The study entitled, "Management of Research Costs: Indirect Costs", was published in May 1992. It identified several options for simplification, standardization, incentives, and the collection of future data.

The changes to A-21, which were published in July 1993, addressed administrative costs primarily. While all of the participants believed that the changes are important, they also acknowledged that the reimbursement of facility related expenditures should be addressed next. There should be standardized methods for the determination of costs which establish reasonable levels of reimbursement for routine expenditures in support of the physical plant so that all parties have confidence in the process without exhaustive staff or administrative effort. To the extent that research investigators, members of Congress, or Federal agency staff do not understand the reimbursement of indirect costs or mistrust the methodology for determining reasonable reimbursement, we will lose public support for research. There is already a prevailing misconception that indirect costs are associated entirely with colleges and universities, OMB Circular A-21, biomedical research, and NIH. In fact, indirect costs are reimbursed to all recipients of Federal grants and contracts, including commercial organizations, hospitals, and non-profit organizations. The determination of those costs are specified in the Federal Acquisition Regulations (FAR) for commercial organizations, HHS policy for hospitals, and OMB Circular A-122 for non-profit organizations.

INDIRECT COSTS ASSOCIATED WITH FACILITIES CONSTRUCTION

Mr. Smith: Do you have any ideas about how to deal with the facilities element of indirect costs, which accounts for a large share of the cost, but varies greatly from grantee to grantee?

Dr. Varmus: As suggested in the previous response, the methodology for determining operations and maintenance (O/M) type expenditures and their proper allocation in the support of research should not be difficult. The approach should not vary substantially when referring to costs of utilities, security, biohazards, etc., at a university or a research institute. The O/M costs make up about 16 points of approximately 24 points for facility related expenditures (16 points O/M plus 8 points depreciation or use allowance) in the average indirect cost rate of approximately 54 points. However, the mechanism for reimbursement for the actual cost of the space is more complex (depreciation/use allowance). Space costs vary given the sophistication of the facility, regional costs of construction, age, design, and so forth. It is very difficult to determine whether a fair methodology for reimbursement should be based on actual depreciation or by a use allowance and whether it should be based on facility-specific costs or some normative standards for research facilities around the country. It is also a difficult public policy question to determine if the costs for new facilities or extensive renovations should be reimbursed through direct cost construction grants, which at least permit a needs assessment, as compared to the institution including whatever the costs may be in rate negotiations. It is for these reasons that there should be a Federal-wide initiative coordinated by OMB to address this area of indirect cost reimbursement.

EXTRAMURAL BIOMEDICAL RESEARCH FACILITIES

Mr. Smith: What is your view of the adequacy of biomedical research facilities in this country and how do needs in this area rank against other problems?

Dr. Varmus: The 1992 Survey of Scientific and Engineering R&D Facilities at Colleges and Universities indicated that about 32 percent of biomedical research institutions responded that their current amount of research space was inadequate, which is a decrease from 41 percent in 1990. Of the inadequate space, 21 percent required limited repair or renovation, 12 percent required major repair or renovation, and 2 percent required replacement. This obviously is a substantial need, which must be addressed within other competing priorities, such as national public health problems (breast cancer, AIDS, Alzheimer's Disease, etc.), training of young investigators, and research instrumentation. It is in the nation's best interest to address the status of research infrastructure on a steady basis over time rather than unpredictable levels of support from one year to the next.

Mr. Smith: What is your current best estimate of NIH direct and indirect support for facilities in 1994?

Dr. Varmus: NIH will award approximately $25.5 million in direct cost construction grants and approximately $274 million for the indirect reimbursement for space costs (depreciation or use allowance).

Mr. Smith: You are experimenting with some changes in the peer review process. Tell us a little more about what you are doing and the perceived problems you are addressing.

How do you propose to handle the pressures to create disease-specific study sections?

Dr. Varmus: NIH extramural programs have been designated as a PHS "reinvention laboratory". All aspects of the grant administration process, from application through peer review, award and post-award monitoring, are being reevaluated. The overall goal, in our determination of scientifically meritorious projects, is to improve the system in terms of accuracy, efficiency and cost-effectiveness, while ensuring that applications receive a thorough review. The fair review of all applications is our guiding principle and we will ensure that any changes considered will not violate that principle.

These activities are, in part, a continuation of NIH's normal reevaluation of its policies and procedures, but are even more critical now because of fiscal constraints and the need to reduce the federal workforce. Over the past 20 years, the number of applications that are reviewed has increased from fewer than 19,000 to over 38,000 in 1993. Neither staffing nor funding has kept pace with this increase. Applicant institutions are facing similar constraints. Since the situation is not likely to improve and may, in fact, worsen, it is necessary that NIH consider all possible measure for improving efficiencies.

There are two major initiatives that are already underway; one having to do with the triage of grant applications and the other with the receipt of certain grant application materials on a "just in time" basis. The triage pilot test will extend the use of triage from the institutes to the Division of Research Grants, and determine the value of identifying applications that are not competitive earlier in the review process, consequently conserving the discussion time of the initial reviewers and the production of a more elaborate review summary. Modifications of the traditional summary statement are also being studied which may allow for more timely return of critiques to the applicants. The "just in time" pilot tests postpones the collection of a fairly substantial amount of information that currently must be provided in all competitive applications and requests that information from only those applicants that are clearly being considered for funding. This delayed request and receipt of information relieves the burden for approximately 70-75% of applicants who will not receive an award.

There are several other important initiatives that are emerging from other committees that will be prioritized for short term tests or potential implementation of administrative simplifications. These topics are being selected on the basis of improvements of services to the research community, enhancements in the stewardship of funds, and increases in administrative efficiencies. The electronic exchange of application and post-award information is the heart of long-term improvements in the current system. These and other potential changes will help keep resources from being absorbed by administration and conserve them for the direct support of research.

PEER REVIEW OF CLINICAL RESEARCH

Mr. Smith: Study findings indicate that clinical research applications do less well in the peer review process than basic research. To what do you attribute this gap, and how are you planning to address it?

Dr. Varmus: The study to which you refer is a pilot survey conducted by the NIH Division of Research Grants (DRG) to determine which study sections review clinical research and to determine the competitive fate of these applications. The results of this survey provided preliminary data for the first meeting in March 1994 of the Clinical Research Study Group. This Study Group is comprised mainly of outside scientists and was assembled to develop and review information concerning the evaluation of clinical research grant applications by DRG's study sections and to provide well-considered advice and recommendations based on their findings.

The preliminary data developed from this survey suggest that clinical research grant applications do not fare as well as basic research grant applications. However, the data also demonstrate that clinical research applications improve markedly upon being revised and resubmitted. We would caution that these data are based on information from only one review cycle and that this survey included a test of definitions to categorize the types of clinical research reviewed in DRG. With the experience of this survey, an expanded study will be conducted in the June review cycle.

The Clinical Research Study Group will be considering these and other quantitative and qualitative data. The experiences, recommendations, and suggestions from clinical investigators will also be obtained by written and oral testimony. It is anticipated that the report of this Study Group will be presented to the DRG Advisory Committee at its November 1994 meeting.

It should be noted that a significant number of clinical research grant applications are submitted to the NIH in response to institutes' solicitations (a Request for Applications); such applications are generally reviewed by ad hoc committees empaneled by the soliciting institute.

NIH OMBUDSMAN TO EXTRAMURAL COMMUNITY

Mr. Smith: You have appointed an ombudsman who spends much of his time traveling across the country meeting with extramural scientists. What sort of concerns is your ombudsman hearing from the scientific community?

Dr. Varmus: I feel very fortunate to have been able to secure the part-time services of Dr. Howard K. Schachman who will serve the NIH as the Senior Advisor for Extramural Initiatives for a period of 130 days. Since Dr. Schachman has had an opportunity to report to me on only one trip that he has taken, I believe that it would be premature for me to draw any major conclusions from his initial findings. I can say, however, that many of the concerns and recommendations expressed to him are similar to those that I have heard from many other sources. These include suggestions for changes in the peer review system that many investigators find to be cumbersome. Perhaps the major concern focuses on the large number of excellent, research applications that the NIH is unable to fund and the concomitant damage to the careers of scientists who may not be able to continue their research because of lack of support. After Dr. Schachman has had an opportunity to consult with more representatives of the grantee community in various parts of the country, I plan to utilize his findings in my overall examination of NIH extramural policy and procedures. I will be happy to share these findings with members of the Committee at that time.

REVISIONS TO THE FINANCIAL MANAGEMENT PLAN

Mr. Smith: We understand that a review of the financial management plan is underway. Where does this effort stand, and can you share any of the recommendations with us?

Dr. Varmus: The financial management plan submitted by NIH to Congress has been in effect since the beginning of FY 1992. It was the intention of this plan to establish certain parameters to guide the funding strategies of the various Institutes and Centers at NIH. The plan instituted specific curbs in the growth of the costs of both competing and non-competing research project grants. Furthermore, it also established an average length of award of four years that would help ensure a predictable turnover of the grants in the research portfolio.

During the two years that the current plan has been in effect, the Institutes and Centers have been encouraged to develop a wide range of portfolio management strategies and policies to limit the average sizes of awards without impeding the scientific progress of their various programs. As experience has accumulated, it has become clear that the Plan can be improved to allow a greater range of management options by the Institutes and Centers while still maintaining essential fiscal controls. Therefore, NIH is presently embarking on a process to develop a revised edition of the plan. The next version will include an articulation of principles that will have longer term applicability and be less specific to annual appropriations priorities.

It is premature at this time to state what the specific recommendations will be. As NIH goes through the process of inviting comments from the Institutes and Centers and from various budget officials, we will develop a better sense of the specific proposals that we would recommend which would be in keeping with the principle of supporting scientifically meritorious research while exercising prudent management of our finite resources.

We anticipate that the revision of the financial management plan would be complete in late summer of 1994.

NIH MANAGEMENT OF FTE REDUCTIONS

Mr. Smith: NIH is slated to lose 712 FTEs from 1993 to 1995. We understand you have a committee working to recommend ways to implement this staffing reduction. What management principles have they outlined to minimize the disruption of this downsizing?

Dr. Varmus: A task group was charged to propose ways that NIH can meet its targeted reductions while accomplishing its mission of conducting and supporting biomedical research. These reductions include not only FTE reductions, but cuts in senior positions (GS-14 and above) and in all supervisory positions. The committee prepared draft recommendations to help the NIH meet these organizational changes by focusing on actions that will better utilize the NIH workforce. Many of the recommendations will address reengineering work techniques, often through the use of new computerized tools.

In addition, the NIH will receive a final report from a distinguished fact finding committee that is reviewing the intramural research program. These recommendations are likely to address consolidating some programs to save administrative expenses, and shifting some resources to the most promising areas of research.

In all of these deliberations, the NIH will approach decision making with a keen awareness of the potential impact these organizational changes can have. Our goal in all cases is to minimize disruption to our programs and to our employees. For example, if we are able to simplify certain administrative programs as a result of de-layering or delegation to line managers, we may need to re-train employees to perform other important tasks, and re-direct their efforts to these areas.

NIH RESTRUCTURING

Mr. Smith: Both the Neurology and the Mental Health Institutes are soon to be without permanent directors. Have you considered the possibility of merging these two Institutes?

Dr. Varmus: The National Institute on Neurological Diseases and Stroke was established to conduct and support research, training, and health information dissemination with respect to neurological disease and disorders and stroke. The purposes of the National Institute on Mental Health are substantially different, focusing on research to treat and prevent mental illness, promotion of mental health, and the study of psychological, social and legal factors that influence behavior. Both Institutes are established in law.

Nonetheless, the issue of merging the two Institutes is one that deserves further review in light of the changing resource levels facing the NIH. The Agency is in the process of examining these issues in general; and we are considering, in this process, how to restructure to make the most effective use of resources to ensure the strongest possible research programs. Among the questions we are examining is whether programs should be combined to improve our effectiveness. We will examine this question more fully during this review process.

RECRUITMENT FOR NIH TOP MANAGEMENT POSITIONS

Mr. Smith: You have five Institute directorships to fill, as well as a number of other vacancies on campus. What progress are you making in completing these personnel selections?

Dr. Varmus: The NIH recently completed the search for the Director of the Warren G. Magnuson Clinical Center; John Gallin, M.D., has been selected for the position. In addition, Alan Leshner, Ph.D., was recently appointed Director of the National Institute on Drug Abuse. We have initiated the search process for several other senior positions; these are at various stages of completion. A leading candidate has emerged for the Director of the National Institute on Neurological Diseases and Stroke, and we are pursuing discussions with that individual. The searches to fill the other vacant directorships have also begun. These searches are conducted on a national basis, and often involve extensive advertising, recruitment and discussions with potential candidates. We would expect these searches to be completed within four to six months.

PROPOSAL TO ESTABLISH NCHGR AS AN INSTITUTE

Mr. Smith: We understand that there has been some interest in elevating the status of the Genome Center to an Institute. Is such a proposal being considered, and what approvals does it require?

Dr. Varmus: NIH is not pursuing the retitling of the National Center for Human Genome Research to an Institute at this time. In the event of such a request; however, the retitling would require approval by the Secretary. In accordance with Title IV of the Public Health Service Act, Section 401(c)(1)(B), the Secretary may establish additional national research institutes after she has provided a 180-day written notice of her determination to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate.

SPECIALIZED RESEARCH CENTERS

Mr. Smith: You were quoted in the trade press as having questioned the merit of the specialized research centers mechanism. A number of NIH Institutes seem to be moving to expand specialized centers. Do you expect to establish any campus-wide policy on the use of this mechanism?

Dr. Varmus: Because of the large number of biomedical scientists who are unsuccessfully seeking support from the NIH for their work, I believe that one of my tasks is to evaluate the merit of those large funding mechanisms that involve high levels of support for long periods of time. I do not believe that an arbitrary NIH-wide limit on the size or number of such mechanisms as specialized research centers is appropriate at this time. Rather, I prefer to examine these centers selectively to determine which ones are fulfilling their roles. Ideally, each of these centers should provide an efficient way to support a group of scientists attacking a disease entity or a biomedical problem area. A center's work should be pointed toward a goal not possible to attain if the same level of resources is utilized in another manner, and the goal must justify the large commitment of these resources. We may find during our evaluation that we should limit the size of, or even eliminate, some of these centers.

SUPPORT FOR BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

Mr. Smith: You are establishing a new Office of Behavioral and Social Sciences Research as required by the reauthorization law. What is the appropriate role of this type of research in the NIH portfolio?

Dr. Varmus: In September, 1993, the NIH submitted to Congress its Implementation Plan for Health and Behavior Research that presents each ICD's appraisal of appropriate research topics and activities and, thereby, the role of behavioral, and social research within each ICD's portfolio. From this document and previous reports to Congress, it can be seen that behavioral and social research has played and will continue to play a vital role by contributing to the NIH's portfolio in three ways.

First, it is part of NIH's efforts to understand the causes of disease and medical conditions, to prevent and treat disease and medical conditions, and to promote health. In this regard, NIH-supported behavioral and social research is investigating biobehavioral mechanisms through which behavioral and social factors affect health; identifying psychosocial risk and protective factors;

studying the development, maintenance and change of health-related behaviors; and developing and evaluating behavioral and social interventions to prevent and treat disease or to promote health.

Second, behavioral and social research is involved in NIH's transfer of technology through its contributions to the design and implementation of clinical trials (e.g., recruitment and retention of participants) and public health information campaigns aimed at lay and professional audiences (e.g., design of communication materials and of means for reaching targeted audiences).

Third, behavioral and social research is part of NIH's basic research portfolio. Just as it is necessary for NIH to support basic research on the biochemistry of cells, so is it essential that NIH, in conjunction with other Federal agencies, contribute to a basic understanding of social and behavioral processes. Such an understanding is required in order for behavioral and social research to fulfill successfully its first two roles.

Mr. Smith: What is your view of the behavioral research NIH has funded in the past?

Dr. Varmus: The NIH has had a long, productive, and beneficial involvement in the support of behavioral and social research, especially as it relates to health. This is documented in the numerous reports to Congress on health and behavior. (The most recent report is November, 1991). I believe that these reports demonstrate the value and potential of behavioral research as a significant contributor to NIH's mission. While great strides have been made, the field of behavioral medicine is still relatively young and its concepts and methods are continuously undergoing improvement and refinement. The NIH needs to encourage and support the maturation of this research, because of the obvious role that social and behavioral factors play in health and disease.

NUMBER OF INTRAMURAL LABORATORIES AT NIH

Mr. Smith: Identify the number and subject matter of the NIH intramural labs by Institute.

Dr. Varmus: As described in the catalog, "Postdoctoral Research Fellowship Opportunities," the investigations in NIH's roughly 250 intramural Laboratories and Branches range from fundamental biochemistry of the cell to behavioral studies on the cognitive development of babies and clinical trials of the optimal use of Taxol in the treatment of ovarian cancer. These Laboratories are configured like small university departments.

The following count of the number of research laboratories and branches in each institute is approximate because some institutes and centers are currently reorganizing.

Institute, Center or Division	Number
Division of Computer Research Technology	6
National Cancer Institute	51
National Center for Human Genome Research	6
National Institute for Nursing Research	2
National Center for Research Resources	2
National Eye Institute	8
National Heart, Lung, and Blood Institute	17
National Institute of Allergy and Infectious Diseases	18
National Institute of Arthritis and Musculoskeletal and Skin Diseases	4
National Insitute of Child Health and Human Development	17
National Institute of Dental Research	8
National Institute of Diabetes and Digestive and Kidney Diseases	21
National Institute of Environmental Health Sciences	18
National Institute of Mental Health	25
National Institute of Neurological Disorders and Stroke	23
National Institute on Aging	10
National Institute on Alcohol Abuse and Alcoholism	4
National Institute on Deafness and other Communication Diseases	8
National Institute on Drug Abuse	7
National Library of Medicine	3
Center For Biologics Evaluation and Research (Food and Drug Administration)	36

The catalog, "Postdoctoral Research Fellowship Opportunities", discussing each of these Laboratories is located in the Office of the Clerk, Rayburn House Office Building.

PROGRAMMATIC ADJUSTMENTS TO EXTRAMURAL GRANTS

Mr. Smith: Identify by Institute the average amount of downward adjustment for research grants 1993-1995.

Dr. Varmus: Although an overall rate of reduction for research project grants (RPGs) can be calculated using a simple comparison of initial review group recommended levels to awarded levels, this arithmetic calculation would not accurately reflect NIH's grant funding situation. NIH now uses policies outlined in "A Plan for Managing the Costs of Biomedical Research," the NIH Cost Management Plan (CMP), in funding RPGs. Before the CMP was developed, Institutes' funding policies typically called for across-the-board reductions of specified percents below recommended levels in order to support a targeted number of grants. In that situation, reporting percents of downward negotiations was clearly meaningful. Now, as suggested by the Committee, the CMP directs Institutes to utilize various strategies to manage increases in grant costs in order to achieve an average cost increase which does not exceed the amount of the Biomedical Research and Development Price Index (BRDPI) over the previous year. Recommended strategies include consideration of the costs of grants of equal merit in selecting grants for funding and negotiations of individual grants, if necessary, to ensure that the average cost increases of each Institute's RPG portfolio do not exceed CMP guidelines. Formulaic across-the-board reductions are not acceptable; rat(er, Institutes refer to rational scientific and administrative choices to guide their grant funding strategy.

RESEARCH PROJECT GRANTS

Mr. Smith: Break out the types of grants in the research project grant category (SBIR, program project grants, etc.) in 1994 and 1995. Identify the number of projected grant applications by these categories 1994-1995.

Dr. Varmus: The driving force of the NIH grant pool is the traditional research grant (R01), which comprises approximately 77 percent (19,315 in FY 1993) of all grant applications received. From FY 1992 to FY 1993 R01 applications increased by approximately 10 percent, at the same rate as the total number of applications received overall by NIH (25,140). Also, SBIR applications (R43, R44) will undoubtedly increase, approximately 15 and 18 percent respectively from FY 1992 to FY 1993. The large increases are due primarily to the increased set-aside mandated by Congress (1.5% of the extramural funding base in FY 1993 and FY 1994). It is expected that a similar increase will occur for SBIRs in future years as well, resulting from the increased set-aside proposed in FY 1995 thru FY 1997. These grants will remain stable thereafter at 2.5% of the extramural funding base. By contrast, however, it would be inappropriate to project grant applications for other grant categories (P01, R29, R35, R37, U01, and U19), as they can vary dramatically from one fiscal year to the next. Influential factors such as economic conditions, new disease areas to be studied, the resurgence of old diseases such as tuberculosis, and high risk research lead to fluctuating increases or decreases among the other grant activities and ultimately the overall NIH support.

Thus, to estimate the anticipated applications for these remaining activities would produce projections that are artificial and unpredictable. Collectively they comprise approximately only 13 percent of the entire success rate base.

NIH ATTRITION RATES

Mr. Smith: What is the NIH attrition rate 1991-1995?

Dr. Varmus: The FY 1991 annual FTP attrition rate was approximately 11%, the FY 1992 annual rate was approximately 8%, and the FY 1993 annual rate was approximately 4.8%. Based on current data available for FY 1994, we estimate the current attrition rate will be 4.4%. We estimate the same rate of 4.4% or slightly less in FY 1995 based on continued operations under hiring restraints.

NIH RECISSION

Mr. Smith: Identify the allocation of the 1994 salaries and expenses rescission by Institute.

Dr. Varmus: The $18,120,000 rescinded from the NIH affected 7 organizational components: NCI, $5,885,000; NIAID, $1,879,000; NICHD, $314,000; NIAMS, $76,000; NCHGR, $1,589,000; NLM, $1,962,000; and OD, $6,415,000.

SUPPORT FOR TUBERCULOSIS RESEARCH

Mr. Smith: Identify tuberculosis spending NIH-wide 1993-1995.

Dr. Varmus: The funding levels for tuberculosis research at the National Institutes of Health was $34,986,000 in FY 1993, the estimates for FY 1994 is $46,658,000 and the FY 1995 President's Budget contains a request for $52,464,000.

NIH VACANCIES AT GS-15 AND ABOVE

Mr. Smith: Throughout the NIH, how many Director, Deputy Director and equivalent staffing positions are unfilled?

Dr. Varmus: The NIH currently has two Institute Director positions vacant, in the National Institute of Neurological Diseases and Stroke (NINDS), and the National Institute on General Medical Sciences. The search for the Director of NINDS is nearly complete. In addition, the Directors of the National Institute on Dental Research, the National Institute on Nursing Research, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases have announced their plans to leave those positions. We are in the process of initiating searches for those positions. Finally, the position of Deputy Director for Intramural Research is vacant, and a search has been initiated to fill that position on a permanent basis.

INSTRUMENTATION AND EQUIPMENT COSTS

Mr. Smith: How much does NIH spend on instrumentation and equipment through its research project grants?

Dr. Varmus: In FY 1993, NIH funded 28,744 research grants for approximately $5.0 billion in direct costs. Of these direct costs, NIH allocated approximately $125.0 million for instrumentation and equipment costs.

INDIRECT COSTS ASSOCIATED WITH FACILITIES CONSTRUCTION

Mr. Smith: How much facility construction and renovation is supported by NIH through indirect costs?

Dr. Varmus: In FY 1993, NIH awarded $1,686.0 million in indirect costs to major colleges and universities. Of this, NIH supported approximately $262.0 million for reimbursement of space costs (depreciation or use allowance).

REDUCTION IN THE NUMBER OF CRADAs

Mr. Smith: The number of CRADAs negotiated appears to be dropping, and it is contended that the reasonable price clause is responsible. How serious a problem is this, and do you have plans to address it?

Dr. Varmus: There is a potential conflict between NIH's statutory obligation to commercialize research results and, thus, its programs to develop partnerships and cooperative efforts with the private sector, and a perceived regulatory role suggested by the reasonable pricing clause. A recent survey of NIH research Institutes revealed that about a dozen drug firms indicated that the pricing clause constituted a major impediment to initiating CRADAs with NIH labs. We believe this survey may reflect industry-wide concern over the pricing clause. While many firms have entered into CRADAs with NIH, we strongly suspect, based upon substantial anecdotal evidence, that there are a significant number of lost opportunities due to reluctance by some companies to even approach NIH because of the reasonable pricing clause. Although we have maintained a good track record in the CRADA arena, we would, of course, prefer to have the widest latitude possible in fostering technology transfer with private sector partners, in the full spirit of the Federal Technology Transfer Act.

In order to facilitate a constructive dialogue with our industrial research partners, the NIH is planning to sponsor a public meeting this June to address issues of concern to our CRADA partners, including the pricing clause. Hopefully, the input from this meeting will help NIH devise strategies to reduce barriers to negotiating and executing CRADAs.

SCHOLARSHIP AND LOAN REPAYMENT PROGRAMS FOR FY 1995

Mr. Smith: Proposed bill language in the Office of the Director account includes a provision for scholarships and loan repayments which is not reflected in the President's Appendix. Is this part of the President's official request?

Dr. Varmus: The FY 1995 President's Budget Appendix contains $234,907,000 for the Office of the Director. Within this amount $1,000,000 was included for the scholarship and loan repayment program.

ORMH AND ORWH FUNDING TO NIH ICDs

Mr. Smith: Identify the funds provided in 1993 by the Office of Research on Women's Health and Office of Research on Minority Health to other Institutes.

Dr. Varmus: In 1993 the Institutes received $7,069,909 from the Office of Research on Women's Health and $48,268,000 from the Office of Research on Minority Health, including funds from the Minority Health Initiative.

Mr. Smith: Break out the 1994 and 1995 uses of the Minority Health Initiative funding.

Dr. Varmus: The table below describes the Minority Health Initiative spending for FY 1994 and FY 1995:

	(Dollars In Thousands)	
	FY 1994	FY 1995
Minority Infant Mortality	$ 5,000	$ 5,000
Minority Children's Health	4,000	7,000
Health Behav of Adolesc Min	5,000	5,000
Health Behav of Young Min Adults	6,000	6,502
Problems of Older Min Americans	2,000	2,000
2-Year/4-Year Bridge Program	5,000	6,000
M.S./Ph.D Bridge Program	5,000	6,000
Pre-College Interventions	2,500	2,500
International Research Opportunities	4,000	4,500
Supplements to ICD Initiatives	3,470	4,000
Minority Research Supplements	2,500	2,500
Gaps in Min Health Research	5,000	7,476
Gaps in Training Min Scientists	7,000	8,000
TOTAL	$56,478	$66,478

EVALUATION OF MINORITY TRAINING

Mr. Smith: Are the results of the first phase of the minority training program evaluation conducted by the Office of Research on Minority Health available?

Dr. Varmus: The first phase of the minority training program evaluation conducted by the Office of Research on Minority Health (ORMH) was completed in June 1993. The ORMH recently released a Phase 1 report which summarizes data available on minority participation in all NIH research and training programs. The report is entitled Assessment of NIH Minority Research/Training Programs: Phase 1 and is available from the ORMH. Phase 2 of the project, which is now underway, will include the delineation of the goals and objectives of the targeted programs, as well as an assessment of the need to develop a tracking system to monitor program effectiveness.

FUNDING FOR SHANNON AWARDS

Mr. Smith: What funding is being provided for Shannon Awards in 1994 and 1995 and from what sources?

Dr. Varmus: In FY 1994 NIH will provide $10 million to support Shannon awards. Of this amount, $6 million will be provided by individual institutes with an additional $4 million in matching funds from the Director's Discretionary Fund (DDF) to continue the co-funding of Shannon awards. FY 1995 funding sources and amounts for Shannon awards are expected to be similar to FY 1994.

DIRECTOR'S DISCRETIONARY FUND

Mr. Smith: Has any funding in the 1994 Director's Discretionary Fund been obligated? If so, for what purpose?

Dr. Varmus: The FY 1994 Rescission was applied to the Director's Discretionary Fund, reducing it to $6.5 million this year. To date, $5.2 million has been committed from the Director's Discretionary Fund. These funds will support Shannon Awards for approximately $4 million, a Director NIH Speaker Series for $50 thousand, a loan repayment program for clinical researchers from disadvantaged backgrounds at $170 thousand, $34 thousand for a forensics research study, and $1,000,000 was provided to the NCI to co-fund an intensive effort to sequence the breast cancer gene.

NIH DIRECTOR'S ONE PERCENT TRANSFER AUTHORITY

Mr. Smith: Was the one percent transfer authority used in 1993; and if so, for what purpose? Has it been used to date in 1994?

Dr. Varmus: In FY 1993, the Director exercised her authority to transfer between appropriations in order to redirect funds toward additional tuberculosis research. Of the $102,179,000 available in one percent transfer authority, $9,200,000 from 18 ICDs was transferred for obligation in 5 separate ICDs. The one percent transfer authority has not been exercised, to date, in FY 1994.

Mr. Smith: Identify the one percent setaside tap by Institute 1994-1995.

Dr. Varmus:

	FY 1994	FY 1995
NCI	$ 9,260	$16,155
NHLBI	5,680	9,780
NIDR	754	1,299
NIDDK	3,183	5,480
NINDS	2,803	4,826
NIAID	4,736	8,267
NIGMS	3,892	6,700
NICHD	2,468	4,285
NEI	1,290	2,222
NIEHS	1,174	2,021
NIA	1,869	3,215
NIAMS	993	1,708
NIDCD	723	1,246
NIMH	2,727	4,709

	FY 1994	FY 1995
NIDA	1,891	3,275
NIAAA	825	1,420
NINR	227	392
NCRR	1,476	2,592
NCHGR	572	1,115
FIC	96	170
NLM	533	1,016
	$47,172	$81,893

TAPS TO NIH BUDGET 1994-1995

Mr. Smith: Identify all the various taps on the NIH budget 1994-1995.

	FY 1994	FY 1995
Program Evaluation:		
Office of the Assistant Secretary	$ 3,000	$ 3,084
Agency for Health Care Policy & Research	9,410	43,200
National Center for Health:		
Statistics	20,578	21,154
Assistant Secretary for Health Planning & Evaluation	9,674	9,945
Sub-total	$ 42,662	$ 77,383
National Research Service Awards:		
Primary Care (HRSA) AHCPR (OASH)	3,734	3,786
DHHS Special Projects	1,035	1,076
PHS Special Projects	5,015	5,215
DHHS Working Capital Fund	8,514	8,917
TOTAL	$ 64,694	$100,164

AIDS DISCRETIONARY FUND

Mr. Smith: Has any funding in the AIDS Discretionary Fund been obligated. If so, for what purpose?

Dr. Varmus: To date, the OAR has obligated approximately $540,000 for the acquisition of 200 *Macaca nemestrina* (pig-tailed macaques). These macaques represent an animal model useful for etiology and pathogenesis studies of HIV infection as well as HIV transmission. The pigtail macaques may offer more research opportunities in HIV studies than other available animal models. These particular animals were purchased prior to an export ban in order to preserve access to this valuable animal model. Other proposals from ICDs that are considered timely and fall within the requirements for discretionary funding are presently under review. Such scientific opportunities include the identification and screening of natural agents identified in unique ecological areas such as the tropical rain forests of South America and the opportunities resulting from the breakthrough findings of the AIDS Clinical Trials Group study 076 which recently demonstrated that AZT administered during gestation and labor and to the infant after birth reduces the rate of HIV transmission. The OAR is presently reviewing requests for discretionary funding of supplements to ICD peer-reviewed grants and peer-reviewed grant applications to support exceptionally innovative research that will not otherwise be funded.

AIDS ONGOING COMMITMENTS

Mr. Smith: How is "ongoing commitment" defined by the Office of AIDS Research? For example, how is it defined with respect to clinical trails and intramural research?

Dr. Varmus: The Office of AIDS Research, in consultation with the Director, NIH and the Division of Financial Management, NIH, have identified "ongoing commitment" to be the items included in the traditional NIH commitment base. This would include the continuation cost of all previously awarded grants, contracts, and training grants. In addition, it would include intramural research and research management and support at the commitment base levels for each Institute, Center, and Division. The OAR has a strong moral obligation to patients on clinical trials and consequently feels that clinical trials which are eligible for competing renewal should be reviewed on a case by case basis to determine their relevance to the overall NIH AIDS program and funding provided as appropriate.

Mr. Smith: Identify other options for the budget presentation of the Office of AIDS Research that were considered and judged to be in compliance with the authorizing statute.

Dr. Varmus: After reviewing the legislation NIH considered several options that would be in compliance with the authorizing statute. These include:

- Option 1 -- A single AIDS appropriation in a new OAR appropriation account. Transfer authority for OAR Director would be included in appropriation language;

- Option 2 -- AIDS funds appropriated to ICDs, but earmarked in appropriation bill language. A general provision in appropriation language would give the OAR Director authority to transfer "such sums" among ICDs to carry out P.L. 103-43 (the NIH Revitalization Act); and,

- Option 3 -- AIDS funds appropriated to the ICDs, with no specific earmark (current process). Transfer authority similar to that of Option II would be requested.

In our view, the direct appropriation with transfer authority-- Option 1 -- best follows the intention of the legislation.

Mr. Smith: For what purpose and under what authorization is the AIDS construction funding allocated in 1993-1995?

Dr. Varmus: In FY 1993-1995 there has not been a request to provide funding for AIDS construction, however the NIH Revitalization Act of 1993 provides general construction authority to the National Center for Research Resources which may be used for AIDS if necessary.

CELL BIOLOGY LABORATORY

Mr. Smith: Is the $3.8 million provided in 1994 the last funding that will be required for the campus cell biology lab?

Dr. Varmus: Yes, the $3.8 million in the FY 1994 Buildings and Facilities appropriation provided sufficient funds to initiate and complete construction of a facility for the expansion of cell biology programs. Additional funds are not required. Construction is expected to be completed in December 1995.

Mr. Smith: Provide the lifetime costs of the following and the year in which they will be complete: Clinical Center maintenance and safety program; infrastructure modernization; power plant safety; asbestos abatement; fire protection/life safety program; and the Rocky Mountain Lab safety upgrades.

Dr. Varmus: The following programs reflect estimated lifetime costs and dates of completion.

LIFETIME COSTS
(DOLLARS IN THOUSANDS)

Program	Total Costs	Estimated Year of Completion	Estimate of Funds Required to Complete (Includes FY 1995 Req.)
Clin Ctr Maint & Safety	$ 73,000	1997	$ 52,100
Infrastructure Modern	210,020	1999	108,795
Power Plant Safety	8,900	1999	6,900
Asbestos Abatement	55,000	2004	49,500
Fire Protection/ Life Safety Program	35,000	2004	33,000
Rocky Mountain Lab Safety Upgrades	13,700	1998	12,700

WILLIAM H. NATCHER BUILDING

Mr. Smith: Identify the total and remaining costs for the William H. Natcher building and the NIEHS building; the years in which the costs occur; obligations incurred to date; and construction schedule.

Dr. Varmus: The total cost of the William H. Natcher Building is projected to be $186.657 million. Appropriations total $130.634 million through FY 1994, and obligations through FY 1994 are estimated to be $98.489 million. The amount of $56.023 million is required for completion. Phase I construction began in October 1992 with occupancy scheduled to begin in October 1994. Solicitation for procurement of Phase II construction has been deferred until the NIH Campus Plan is approved by the National Capital Planning Commission, currently estimated for September 1994.

The total cost of the program and support facilities at the NIEHS, Research Triangle Park, is estimated at $66.890 million. Total appropriations through FY 1994 are $33.990 million, and estimated obligations for the same period are $29.826 million. Funds of $32.9 million are required for completion. Construction contracts for four of the five phases of the laboratory addition were awarded in FY 1993. The $10.0 million requested in FY 1995 will provide for the continuation of the laboratory module construction. The remainder of the funds required ($22.9 million) will complete the laboratory module and fully fund the construction of the administrative module.

UHSUS AS AN INTRAMURAL FACILITY FOR NIH

Mr. Smith: What are the possibilities of using the Uniformed Health Services University space for NIH intramural activities if it were to become available?

Dr. Varmus: The Uniformed Health Services University space could be used by NIH for research, administrative offices, and parking. This space would require significant cost investments for upgrade of its systems to the level required to support NIH research programs.

INTEGRATION OF BASIC SCIENCE DISCIPLINES

Mr. Porter: Approximately two years ago as part of the strategic plan, the NIH adopted the "integrative medical sciences" as a priority area of research. What progress has been made in restoring funding to this major area of research enterprise? What additional measures will be implemented in the next fiscal year?

Dr. Varmus: The integration of different basic science disciplines and fundamental research from different categorical Institutes has the potential to accelerate progress in biomedical research. One way in which I have encouraged such integrative medical sciences in the Intramural program at NIH has been to support the establishment of six major Inter-Institute Interest Groups--Neurobiology, Genetics, Structural Biology, Molecular Biology, Cell Biology, and Immunology. These groups bring scientists together from all of NIH's Centers, Institutes, and Divisions to focus on basic research questions that cut across institutional boundaries.

Mr. Porter: What steps has the NIH taken to assure that policy makers understand the critical significance of integrative biomedical sciences?

Dr. Varmus: Beginning at my confirmation hearing, I have repeatedly and pointedly stressed that basic, integrative research is central to the continued excellence of biomedical research in the United States. On January 31 and February 1 of this year, I helped organize the Forum on Science in the National Interest at the National Academy of Sciences, as requested by President Clinton. The purpose of this meeting was to bring together scientists and the most senior-level policy makers to document and summarize the importance of fundamental research for President Clinton. In addition to distinguished scientists, Vice President Gore and several members of Congress attended. A report of the meeting is now almost ready for the President's signature. I will continue to make the case for integrative research through interactions with top Executive Branch policy-makers as a co-chair of the Committee on Fundamental Science of the President's National Science and Technology Council.

Mr. Porter: For each basic science discipline, how many pre-doctoral students are receiving NIH funding for research at the level of the intact animal; how many post-doctoral students? What percentage of the total number of students receiving NIH training fellowships do these students represent? How does this impact the future of integrative biology?

Dr. Varmus: The absence of readily accessible data does not allow an immediately definitive answer to the questions you pose. However, we are able to make reasonable estimates by combining certain currently available data, historical ratios, and minimal assumptions. The following technical discussion describes the calculation strategy. Accompanying tables provide the detailed calculations and results.

ALGORITHM FOR
ESTIMATING THE NUMBER OF PREDOCTORAL AND POSTDOCTORAL TRAINEES INVOLVED IN RESEARCH PROJECTS USING ANIMALS

Calculations begin with the known total number of FY 93 NIH-supported research grants - 30,975. Current data allow this number to be broken down into awards to basic science departments and all other departments of recipient institutions of higher education (IHEs) for R01, P01 and all other research awards. Such departments were used as an available proxy for basic science areas. On this basis the estimated number of awards to each basic science and all other areas for non-IHE recipients were distributed by using the calculated ratios of IHE department totals to all IHE awards. The resulting figures can be found in Table 1.

Data available from the National Center for Research Resources suggests that forty percent of all NIH research grants involved the use of intact animals (the exact category was mammals, which excludes non-mammalian vertebrates) in one way or another. This ratio was applied to the figures in Table 1 to arrive at an estimate of the numbers of FY 1993 research projects by basic science area and all other areas involving the use of animals. See Table 2.

A recent NIH study ("Staffing Patterns of the National Institutes of Health Research Grants",1993) looked into the involvement of predoctoral and postdoctoral trainees involved in NIH-supported research projects. It concluded that the average predoctoral FTE (full-time equivalent) on an NIH research grant was .41. The corresponding postdoctoral figure was .39. Applying these estimates to the number of awards in Table 2 (projects involving animals) allowed a calculation of the estimated number of predoctoral and postdoctoral trainees involved with projects using animals in the research process. Those numbers are detailed in Table 3.

The figures in Table 3 provided the basis for these calculations. It is estimated that 5,080 FTE (full-time equivalent) predoctoral and 4,832 FTE postdoctoral trainees participated in 12,390 NIH-supported research projects involving animals in FY 1993. Forty-four percent of these trainees, or 4,370, (representing approximately a one-third of all NIH supported trainees) were engaged in research projects in basic science areas, including biochemistry, biology, microbiology, pharmacology, and anatomy. The estimated numbers of pre- and post-doctoral trainees for each of the basic science areas are detailed in the attached Table 3.

The data suggests that at least 9,912 predoctoral and postdoctoral trainees in FY 1993 were involved in NIH-supported research projects in which animals were used. This has provided, for a considerable number of current and future bioscientists, important exposure and training with regard to the role of animals in research. Additional trainees will obtain similar experience in the future. We believe this plays an important role in shaping appropriate uses of animals in all types of biomedical research including integrative biological research.

TABLE 1

NUMBERS OF FY 1993 RESEARCH GRANTS BROKEN OUT BY BASIC SCIENCE AND ALL OTHER DISCIPLINES, TYPES OF GRANTS AND INSTITUTION OF HIGHER EDUCATION STATUS

		BASIC SCIENCE DISCIPLINES													
	FY 93 TOTAL	Anatomy	Biochem.	Biology	Biophys.	Chemistry	Genetics	Microbio.	Other Basic Sci.	Pathol.	Pharmacol.	Physics	Physiol.	Zoology	All Non-basic Science
R01 Grants IHE	15,340	695	1,310	933	94	830	300	890	219	623	881	32	865	129	7,539
R01 Grants NOT IHE	3,335	151	285	203	20	180	65	193	48	135	192	7	188	28	1,639
P01 Grants IHE	701	26	35	35	7	3	12	29	8	33	38	0	49	3	423
P01 Grants NOT IHE	222	8	11	11	2	1	4	9	3	10	12	0	16	1	134
Other Grants IHE	8,364	190	397	466	28	312	73	276	95	281	330	21	257	63	5,575
Other Grants NOT IHE	3,013	68	143	168	10	112	26	99	34	101	119	8	93	23	2,008
All research grants	30,975	1,139	2,181	1,816	162	1,439	480	1,497	406	1,184	1,571	68	1,467	247	17,318

IHE=Institutions of Higher Education
NON-IHE=Other than Institutions of Higher Education

TABLE 2

NUMBER OF NIH RESEARCH PROJECTS INVOLVING ANIMALS

For FY 93 0.4	FY 93 TOTAL	BASIC SCIENCE DISCIPLINES Anatomy	Biochem.	Biology	Biophys.	Chemistry	Genetics	Microbio.	Other Basic Sci.	Pathol.	Pharmacol.	Physics	Physiol.	Zoology	All Non-basic Science
R01 Grants IHE	6,136	278	524	373	38	332	120	356	88	249	352	13	346	52	3,016
R01 Grants NOT IHE	1,334	60	114	81	8	72	26	77	19	54	77	3	75	11	656
P01 Grants IHE	280	10	14	14	3	1	5	12	3	13	15	0	20	1	169
P01 Grants NOT IHE	89	3	4	4	1	0	2	4	1	4	5	0	6	0	54
Other Grants IHE	3,346	76	159	186	11	125	29	110	38	112	132	8	103	25	2,230
Other Grants NOT IHE	1,205	27	57	67	4	45	11	40	14	40	48	3	37	9	803
All research grants	12,390	456	872	726	65	576	192	599	163	474	629	27	587	99	6,927

IHE=Institutions of Higher Education
NON-IHE=Other than Institutions of Higher Education
Animals=mammals excluding non-mammalian vertebrates

TABLE 3

ESTIMATED NUMBER OF PRE AND POST DOCS
INVOLVED IN NIH RESEARCH PROJECTS USING ANIMALS

0.41 0.39	FY 93 TOTAL	BASIC SCIENCE DISCIPLINES													All Non-basic Science
		Anatomy	Biochem.	Biology	Biophys.	Chemistry	Genetics	Microbio.	Other Basic Sci.	Pathol.	Pharmacol.	Physics	Physiol.	Zoology	
R01 Grants															
Predocs	3,063	139	262	186	19	166	60	178	44	124	176	6	173	26	1,505
Postdocs	2,913	132	249	177	18	158	57	169	42	118	167	6	164	24	1,432
P01 Grants															
Predocs	151	6	8	8	2	1	3	6	2	7	8	0	11	1	91
Postdocs	144	5	7	7	1	1	2	6	2	7	8	0	10	1	87
Other Grants															
Predocs	1,866	42	89	104	6	70	16	62	21	63	74	5	57	14	1,244
Postdocs	1,775	40	84	99	6	66	15	59	20	60	70	4	55	13	1,183
Total Predocs	5,080	187	358	298	27	236	79	246	67	194	258	11	241	40	2,840
Total Postdocs	4,832	178	340	283	25	224	75	234	63	185	245	11	229	38	2,702
Total Predocs (Basic Sciences)		2,240													
Total Postdocs (Basic Sciences		2,130													

Animals=mammals excluding non-mammalian vertebrates

SUPPORT FOR BASIC SCIENCE DISCIPLINES

Mr. Porter: What do you see as the ideal for the NIH grant portfolio as far as percentage of projects in molecular, cellular, systems and intact animal areas? Why?

Dr. Varmus: Molecular, cellular, system, and animal studies are all fundamental to the mission and mandate of the NIH. These four areas collectively serve to advance an overall understanding of biology and its application to improving human health. Because the four areas are all of crucial importance and because knowledge gained in one advances the others as well as all of biomedical and behavioral research, it is difficult to measure in a relative way the contributions each single area makes to the advancement of science and human health.

The guiding principles determining the composition of the NIH grant portfolio in these areas, and in all areas, are scientific opportunity and scientific merit. Thus, the "ideal" balance is a fluid one, arrived at in the course of merit reviews of grant applications; it is not appropriate to establish pre-determined percentages or ratios. This longstanding funding policy is rational, fair, and efficient, and it has enabled us to advance science and to pioneer discoveries in a range of diseases. It also has served as a policy model for other Nations and has been the basis for U.S. dominance in biomedical and behavioral research.

GRANT PEER REVIEW IN NIAAA, NIDA AND NIMH

Mr. Porter: When NIAAA, NIDA and NIMH IRGs are dissolved, what changes will you recommend for operations and composition of study sections for DRG in order to maintain the integrity of the grant portfolios of these Institutes? How will an appropriate balance of funding be enforced?

Dr. Varmus: First, it is likely that some initial review groups (IRGs) will remain in NIAAA, NIDA, and NIMH. As with all other institutes and centers at NIH, these three institutes will retain certain IRGs to carry out the review of some institute-specific applications such as those for research centers, program project grants, and cooperative agreements. The bulk of the applications can, however, most appropriately undergo peer review centrally within the NIH's Division of Research Grants (DRG). The review of these applications in DRG may be accommodated in several ways. It is possible that some applications will be assigned to existing DRG study sections with the addition of only one or a few reviewers to provide additional expertise. More likely, however, is that existing DRG study sections will need significant expansion, that new study sections would be created, and that some NIAAA, NIDA, and NIMH IRGs would be transferred nearly intact to the DRG. To the degree possible, and with the agreement of the members of those IRGs, they would be invited to become members of these new DRG study sections. These changes would be accomplished after extensive consultation with the staff of the three institutes.

The issues of maintenance of grant portfolios and funding balance are issues common to all NIH institutes and centers. For many years, the determinations of scientific merit (by IRGs) and funding (by advisory councils/boards and institute program staff) have been separate. The recommendations of the IRGs are considered by the institute advisory bodies and staff and they represent only one of the elements that enter into a funding decision. This authority and responsibility permits the institutes to develop and maintain their grant portfolios and to adjust portfolio balance regardless of the mechanism of support and the site of peer review.

RECRUITMENT OF RESEARCHERS IN INTEGRATIVE MEDICINE

Mr. Porter: I understand that few researchers in integrative biomedical sciences are being trained while current investigators in this area are retiring. What mechanism has been designed to assure the Nation of an adequate supply of integrative biomedical scientists?

Dr. Varmus: More than 3,500 or half of the graduate students supported by National Research Service Awards (NRSA) train in programs considered to be multidisciplinary often spanning several departments within particular graduate schools. The focus of these studies is on integrative biology. Students learn the advantages of using various experimental approaches to health related problems including molecular, cellular, and intact animal systems. The National Academy of Sciences in its new report Meeting the Nation's Needs for Biomedical and Behavioral Scientists has considered retirements and other factors for several components of the academic sector. This report does not identify a pending human resource shortage in any biomedical area.

PROGRESS OF NATIONAL CENTER FOR SLEEP DISORDERS RESEARCH

Mr. Porter: Now that the National Commission on Sleep Disorders Research has released its report and the National Center for Sleep Disorders Research has been established, how well do you think the Center is doing in carrying out the recommendations of the Commission?

Dr. Varmus: The National Center on Sleep Disorders Research (NCSDR) is off to an excellent start and is making good progress towards implementing some of the recommendations in the report of the National Commission on Sleep Disorders Research. In addition to establishing the National Center on Sleep Disorders Research, the Commission report recommended strengthening and expanding ongoing research and training programs; developing professional and public education programs on sleep and sleep disorders; and coordinating sleep disorders research across the federal government.

The NCSDR has taken the lead in developing a NIH-wide program announcement on sleep, which identifies many new basic and clinical sleep research opportunities which should stimulate research in this multi-disciplinary field. Applications responding to this program announcement will strengthen and expand ongoing sleep research at NIH.

The Center has other initiatives underway as well. The NCSDR is soliciting applications for a new program to study the cardiovascular consequences of sleep apnea, which should provide new information on the important question of whether sleep apnea is a independent risk factor or contributing risk factor for the development of cardiovascular disease. To address the sleep education report recommendations, the Center has planned a workshop that will develop a strategy for a national education program. The workshop will provide recommendations for both public and professional education and the Center is hopeful that other federal agencies, professional and voluntary organizations will help implement some of the recommendations beginning in FY 1995. In addition, the NCSDR is working with the National Institute on Child Health and Human Development on a public awareness campaign related to sleep position (stomach versus side or back) and its relationship to Sudden Infant Death Syndrome.

Mr. Porter: Dr. Varmus, a key recommendation of the National Commission that was included in the authorizing legislation was that the National Center would help coordinate activities with other agencies. Do you believe that the Center has been/will be successful in coordinating sleep activities conducted among many Federal agencies?

Dr. Varmus: Yes, the National Center on Sleep Disorders Research (NCSDR) has already initiated collaborations with other agencies and anticipates more in the future. For example, the NCSDR is currently working with NASA to develop joint programs in sleep, prolonged shift work, human performance, sleep loss and fatigue both on earth and in the microgravity environment.

The development of a national education program will require collaboration among Federal agencies. For example, participants in the workshop this summer include representatives from the Department of Transportation, Department of Defense, Department of Veterans Affairs, Department of Commerce, Department of Labor, Centers for Disease Control and Prevention, and the National Aeronautics and Space Administration. The workshop will provide recommendations for both public and professional education to be implemented across Federal agencies.

The NCSDR is also working with the Federal Highway Administration to assist with the scientific and technical review of a proposal to examine the incidence of sleep apnea in commercial motor vehicle carriers. We anticipate this effort will address research issues related to sleepiness, fatigue and sleep disorders as factors in traffic accidents.

Lastly, we recently appointed members and ex officio representatives to the Sleep Disorders Research Advisory Board. The Board, which includes ex officio members from a number of Federal agencies, will assist the NCSDR in identifying research priorities, developing plans, and coordinating sleep and sleep disorders research across the Federal government. The first meeting of the Board will take place in the summer of 1994.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. Which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly. How much is included in the FY 1995 budget request for gene therapy? How much did NIH invest in this research in FY 1994 and FY 1993?

Dr. Varmus: Gene therapy offers hope to the millions of people not only in the United States but worldwide who are afflicted with a genetic disease or condition. The NIH invests heavily in research on identifying and isolating the genes that cause hereditary diseases and disorders. Support is also provided for research on the underlying mechanisms that need to be understood to make gene therapy possible such as: hematopoietic stem cell biology, cell line and animal model development, vector development, development of molecular techniques for transfer of genes to specific locations on DNA, methods for insertion of genes into various types of somatic cells, and specific methods for therapy of particular diseases.

The basic research findings are now being applied to clinical protocols of gene therapy in patients who have Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase Deficiency (ADA), Cystic Fibrosis, Familial Hypercholesterolemia, and Gaucher's Disease.

Gene therapy is also being explored as a methodology for treatment of diseases which are not hereditary. Examples are research to enhance the body's resistance to infection by the AIDS virus, as an alternative to vaccines. In the area of cancer research, scientists are trying to improve the body's natural defenses against the disease or to increase the effectiveness of chemotherapy by manipulating the genetic makeup of specific cells.

During FY 1993 the NIH obligated approximately $132,228,000 for gene therapy research. FY 1994 and FY 1995 estimates are $150,775,000 and $168,391,000 respectively.

VACCINE DEVELOPMENT

Mr. Stokes: How much is included in the FY 1995 request for vaccine development? How much did NIH invest in this research in FY 1994 and FY 1993?

Dr. Varmus: The FY 1995 President's Budget contains $342,740,000 for vaccine development. The amounts invested to this research in FY 1993 was $253,344,000 and the estimate for FY 1994 is $316,793,000.

MINORITY HEALTH

Mr. Stokes: As the new director of the nation's principal federally-supported biomedical research investment, how would you respond to the statement...The Minority Health Crisis Continues...while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Varmus: I recognize that the health of many minority Americans has deteriorated despite advances in medical knowledge. In addressing this health gap, it is imperative that two issues be addressed.

First, I will work to identify the underlying causes of the minority health crisis -- the diseases, dysfunctions, and conditions that disproportionately affect minorities. Then, I will work to expand and strengthen the Minority Health Initiative (MHI), a multi-component minority health research and research training program which Congress first funded in Fiscal Year 1993. As you are well aware, the MHI is a comprehensive program designed to improve minority health across the lifespan. In collaboration with specific NIH Institutes, the Office of Research on Minority Health (ORMH) administers the MHI. The ORMH has worked with the Institutes to launch programs that address health issues from birth to old age. The MHI provides funds that the Institutes need to launch significant new minority health research efforts.

Second, minority health issues cannot be divorced from those of minority research training. The health status of minorities is not unrelated to the underrepresentation of minorities in the biomedical sciences. Therefore, as NIH takes steps to educate the next generation of health scientists, it has placed a special emphasis on training minorities. In addition to the health component, the MHI also supports programs that address the science education and training needs of minorities at all stages of the educational pipeline--from pre-college to post-graduate.

Mr. Stokes: As the new director for the nation's premier biomedical research enterprise, what are your plans for closing the minority health disparity gap?

Dr. Varmus: By aggressively addressing both the health disparities experienced by minorities and their underrepresentation in the biomedical and behavioral sciences, the NIH is taking positive steps toward eliminating the health disparity gap.

RECENT ORGANIZATIONAL CHANGES

Mr. Stokes: As the new director of the National Institutes of Health, have you made any significant organizational changes thus far? If so, elaborate.

Dr. Varmus: I have forwarded two significant organizational changes for approval by the Secretary since I became NIH Director--specifically, the establishment of the (1) National Center for Sleep Disorders Research within the National Heart, Lung, and Blood Institute; and (2) Office of Behavioral and Social Sciences Research within the Office of the Director, NIH. Both of these components were mandated by the NIH Revitalization Act of 1993 (P.L. 103-43), and are discussed below:

Section 503 of Title V pertains to the establishment of the National Center for Sleep Disorders Research within the National Heart, Lung, and Blood Institute to provide a national focus for sleep disorders research. The Center's general purposes will be the (1) conduct and support of research, training, health information dissemination, and other activities related to sleep disorders, including biological and circadian rhythm research, basic research to enhance understanding of sleep, chronobiological and other sleep related research; and (2) coordination of the activities of the Center with similar activities of other Federal agencies, including other NIH Institutes; and similar activities of other public and nonprofit entities.

As required by Section 203, the Office of Behavioral and Social Sciences Research will be responsible for (1) advising the NIH Director and other key officials on matters pertaining to behavioral and social sciences research; (2) coordinating research in the behavioral and social sciences conducted and supported by the NIH institutes and centers (IC); (3) identifying research projects that deserve expanded effort and support by the ICs; and (4) developing research projects in cooperation with the ICs.

Research in the behavioral and social sciences contributes to a better understanding of ways to enhance human health and to prevent, treat, and cure disease. Most NIH institutes and centers conduct and support basic and clinical research to determine how individual, familial, social, and environmental factors interact with relevant biological issues. Consequently, there is a critical need for an NIH Office to evaluate these activities and to develop an overall strategy to improve the health and well-being of the people of the United States.

OPPORTUNITIES IN BASIC RESEARCH

Mr. Stokes: What are some of the most exciting basic research opportunities at the NIH?

Dr. Varmus: A sample of some particularly promising areas of research is presented below. These areas reflect NIH's commitment to carry out research that will accelerate progress in the fundamental sciences and biomedical technologies, enhance disease prevention efforts, lead to improvements in the health and well-being of Americans, and strengthen the ability of the Nation's biomedical research enterprise to respond to current and emerging public health needs.

Cardiovascular Disease and Stroke:

Unraveling Cardiovascular Disease Processes. Vascular problems such as atherosclerosis and hypertension cause cardiovascular disease, the leading cause of death and disability among Americans. The total economic burden of this disease exceeds $100 billion per year. From earlier studies on the progression of atherosclerosis, we know that smooth muscle cells migrate from their normal position in the vessel wall to the interior of the vessel where they proliferate and obstruct blood flow. Now scientists have learned that as smooth muscle cells age, they produce enzymes that destroy the normal vessel architecture. This facilitates the migration of the muscle cells, allowing them to become highly invasive. During this process, the smooth muscle cells change their physical and functional properties. Investigators are currently characterizing compounds that might stabilize such cellular changes. These compounds may lead to the development of effective new therapies to reduce and prevent vascular disease.

Cancer.

Elucidating Cancer Causing Mechanisms. One mechanism by which the growth of cells and organs is regulated is by a process known as apoptosis, or programmed cell death. Investigators have recently learned that one of the ways DNA tumor viruses cause cancer in animals is by interrupting the normal process of apoptosis. Oncoproteins (cancer-causing proteins) from Epstein-Barr virus, adenovirus, and herpes simplex virus I all appear to cause cancer in this way. Since apoptosis is important in humans as well as animals, studying these cell culture models could help scientists design novel approaches to prevention and treatment of human cancer.

HIV/AIDS

Deciphering the Disease Mechanism of HIV Infection. Researchers have made some key discoveries about the early stages and progression of HIV infection that have important implications for therapeutic regimens. Previously it was thought that after initial infection with HIV, the virus that causes AIDS, most patients entered a prolonged period during which the virus did not replicate. Recent studies have shown that this is not the case. In fact, while there is a period when HIV is difficult to detect in circulating lymphocytes, extensive active viral replication is occurring within the lymphoid organs throughout all stages of the infection. Other scientists learned that during HIV infection the immune system goes through phases of activation and suppression, an important consideration in designing potential therapies. These studies have yielded crucial information that will serve as the basis for the development of effective therapeutics and vaccines to control, treat and prevent HIV infection and its sequelae.

Chronic Diseases

Repairing Damaged Heart, Brain and Nerve Cells. Several recent studies have opened up new avenues of research that may one day lead to successful treatment of the currently disabling and often permanent effects of cardiovascular disease, stroke, neurological disease, and head and spinal cord trauma:

When the heart is damaged due to cardiovascular disease or heart attack, the impairment is permanent because the cardiac muscle cells (myocytes) are unable to reproduce. Recently scientists have taken a critical first step towards repairing cardiac damage by successfully inducing adult mammalian myocytes to multiply.

Recent progress in the neurological sciences offers the first potential to prevent nerve cell degeneration in such disorders as amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) and Huntington's disease, and to repair nerve cells damaged by head and spinal cord injury and stroke. Researchers demonstrated, in animals, that ciliary neurotrophic factor prevents degeneration and atrophy of damaged brain cells, increases the expression of receptors for nerve growth factor, and induces sprouting of motor nerve cells.

In other promising studies, fibroblast cells genetically engineered to produce nerve growth factor have been implanted into animals and have promoted survival and regeneration of a specific set of brain cells.

Neurological Disorders

Discovery of First Genetic Risk Factor for Alzheimer's Disease (AD). Researchers have determined that the E4 variant of a blood protein known as ApoE is a major risk factor for late-onset AD, the most common form of the disease. While only about 10% of the general population have the E4 type, among late-onset AD patients, E4 was found at a frequency of 40-45%. This implies that the risk of developing AD is increased about three-fold in individuals who inherit ApoE4. Another recent finding suggests that ApoE3 (found in 90% of the population) protects against abnormal changes in proteins that lead to tangles associated with AD, whereas ApoE4 leaves these proteins unprotected. This new information may lead to improved diagnostic methods and the development of effective therapies for the millions of Americans who suffer from AD.

Genome Research and Gene Therapy

Gene Therapy for Cystic Fibrosis (CF). Recent research progress promises improved treatments--and, ultimately, a cure--for cystic fibrosis (CF). The discovery of the gene responsible for CF, known as CFTR, has paved the way for the development of genetic therapy approaches to arrest or reverse CF. In successful earlier studies, scientists genetically engineered a virus that shuttled the normal CFTR gene into cultured lung cells from human CF patients, correcting the defect. In the next phase of research, testing the approach in animals, investigators succeeded in expressing the human CFTR gene in the lungs of rats, and determined that even low levels of expression may be sufficient to correct the defect *in vivo*. The studies have now advanced to the clinical testing stage. Five protocols for gene therapy of the respiratory manifestations of CF have been approved by the NIH and are under way.

Discovery of Novel Genetic Mutation. Data from the Human Genome Project have led to the discovery of a new type of mutation in several disease genes. After analyzing the sequences of the genes responsible for Huntington's Disease, fragile X syndrome, spino-bulbar muscular atrophy (Kennedy Disease), and myotonic dystrophy, scientists noticed a difference between the sequences of affected and unaffected individuals. The genes from affected individuals contained a significantly larger number of repetitions of a set of three DNA bases at a particular site in the gene. The abnormally repeated triplets are thought to disrupt the proper functioning of the gene, resulting in disease. For some of these diseases, the extent of the mutation explains the increase in severity or earlier onset of an inherited disease in successive generations. Since this discovery, a number of other triplet repeats have been isolated from human DNA and their involvement in other diseases, such as bipolar affective disorder, is currently under examination.

Vaccine Development

New Vaccine Technologies. Researchers have made recent significant advances in new vaccine candidates for a number of diseases, including genital herpes and viral-induced diarrhea:

Genital herpes is a common sexually transmitted disease and over 20 percent of adult Americans are infected. Preliminary results from the first human studies of a genital herpes vaccine showed it to be safe and induce substantial immunity to the herpes virus, and its use was associated with reduced rates of recurrent infections. This was the first study in which a vaccine was used to successfully treat a chronic infection.

The most common cause of severe diarrhea among children is the rotavirus. Worldwide, an estimated 140 million cases occur each year, causing almost 1 million deaths. Approximately 3.5 million cases occur in the U.S. annually. Now scientists have demonstrated that rotavirus strains lacking certain outer proteins may confer immunologic protection without causing disease. These strains may be excellent vaccine candidates to prevent this disease.

Novel approaches to vaccine design are also being explored. Studies are being conducted to test whether "naked genes" from a disease-causing microorganism are capable of stimulating the immune system to recognize and reject the pathogen. Although in the early stages, this work has the potential to greatly improve and expand vaccination programs by creating vaccines that are more stable and thus do not require refrigeration, as well as by producing vaccines which may confer immunity with a single inoculation.

Tuberculosis

Rapid Diagnostic Tests for Tuberculosis (TB). TB has re-emerged as a National health threat. Because of the slow growth rate of the TB organism, current tests to diagnose TB and screen for effective drugs take many weeks to complete, during which time the patient may be receiving inappropriate therapy and may transmit the disease to others. Scientists have recently developed two new methods for rapidly identifying TB and screening for effective antibiotics. The diagnostic assay uses PCR technology, which allows very small amounts of DNA to be amplified. The key to the assay is the ability to detect, through PCR, a fragment of TB DNA that is unique to the TB organism. An equally important feature of this method is that TB can be assayed directly from clinical specimens such as a sputum samples, and results can be obtained within 36 hours as opposed to several weeks.

A new antibiotic sensitivity screening process using luciferase, the enzyme that causes fireflies to glow, has abbreviated the assay time from weeks to approximately five days. The process is more sensitive in detecting resistant strains, and has the potential for automation, so that large numbers of samples can be processed in a short time. This method can also be adapted to screen large numbers of potential anti-TB drugs.

Prevention Research

Prevention Research Initiative. A comprehensive program of prevention-directed research will advance our understanding of disease causation and provide insights in applying this knowledge to prevent disease.

PRIORITIES OF THE ORMH

Mr. Stokes: How does the Office of Research on Minority Health identify its priorities for minority research and research training?

Dr. Varmus: The ORMH consults two different groups in formulating its priorities: the minority community and the Institutes, Centers, and Divisions (ICDs) of the NIH.

Minority Community. The ORMH has always sought the advice of members of the minority community in formulating its agenda. When the Office was first established, the ORMH selected a Fact Finding Team which held three regional meetings to assess NIH programs and make recommendations for increasing attention to minority health research issues and for enhancing the numbers of biomedical scientists. The recommendations made by the Fact Finding Team serve as the basis of the ORMH agenda.

Because of the success of the original regional meetings, the ORMH hosted a national conference on March 27-29 in Chicago to inform the minority community of ORMH activities, to allow them to assess the Office's success in responding to the recommendations of the Fact Finding Team, and to solicit additional recommendations for improvements to its agenda. An Assessment Team is currently preparing an addendum to the original Fact Finding Team Report.

NIH Institutes, Centers and Divisions. While the minority community can identify pressing health and training needs, the ORMH relies upon the ICDs to translate those needs, ideas, and recommendations into "good science". All grants must be reviewed by the ICDs in accordance with legally mandated scientific review procedures. Before funding any proposals, the ORMH relies on the ICDs' scientific experts to identify those programs which most likely will yield scientifically valid results--results which have the potential to improve the health of minority Americans and increasing their representation in scientific careers.

Mr. Stokes: When the Office of Research on Minority Health provides funds to the NIH Institutes, Centers, and Divisions, do these funds typically augment existing minority programs or efforts, or do they replace funds previously provided by the Institutes, Center, and Divisions?

Dr. Varmus: The Office of Research on Minority Health (ORMH) leverages its funds in partnerships with the Institutes, Centers, and Divisions to supplement existing efforts and launch new initiatives. For example, in Fiscal Year 1993 the ICDs contributed $130.5 million to jointly funded projects with the ORMH. The ORMH contributed $49.8 million, which includes $40.8 million from the Minority Health Initiative, for a total of $180.3 million. This resulted in an increase in jointly funded minority projects of $84.3 million over Fiscal Year 1992. Furthermore, the ICDs increased their contributions by $44.7 million, or 52% over FY 1992.

Mr. Stokes: When the Institutes, Centers, and Divisions are developing new minority initiatives, do they seek advice from the Office of Research on Minority Health? Elaborate.

Dr. Varmus: One of the strengths of the Office of Research on Minority Health (ORMH) is the strong linkages it has been able to form with the minority community. In the three years since the Office was established, the ORMH has successfully listened to the concerns and recommendations of the minority community and shared that input with the Institutes, Centers and Divisions (ICDs). The evolving partnership between the minority community, the ORMH, and the ICDs has resulted in the implementation of several new important minority health and training initiatives. Examples of the programs the ICDs have established in consultation with the ORMH include the Minority Infant Mortality Initiative, the Bridges to the Future Program, and the Minority International Research Training Program, and the Minority International Research Training Program. As the ORMH continues to gather information from the minority community, it will be even better situated to offer advise to the ICDs as they develop new minority initiatives.

Mr. Stokes: Does the Office of Research on Minority Health have the authority and resources necessary to carry out its multiple responsibilities?

Dr. Varmus: In the three years since the Office of Research on Minority Health was established, it has successfully piloted a number of programs that address both minority health research and research training. Because the ORMH is committed to the full implementation of only the most successful programs, it has incorporated strong evaluation mechanisms in each of the pilot initiatives. As the ORMH continues to pilot new programs, to evaluate the success of those pilots in meeting their health or training goals, and to fully implement those programs that are determined to be successful, the Office may require additional resources.

ORGANIZATIONAL SCOPE OF THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

Mr. Stokes: Does the Office of Research on Women's Health function as a trans-NIH office just like the AIDS trans-NIH office, explain.

Dr. Varmus: Like the Office of AIDS Research (OAR), ORWH is a trans-NIH office within the Office of the Director, National Institutes of Health (NIH). ORWH has many aspects of action similar to OAR, but differs markedly in budget management, beginning in FY 1994. The NIH Revitalization Act of 1993 calls for OAR to develop a comprehensive research plan and requires that the Plan serve as the basis for a single NIH AIDS appropriation within the FY 1995 President's budget which will be distributed to the institute and center directors based on the development of such a plan. Alternately, ORWH has a budget which, when coupled with monies from the NIH institutes and centers, targets the development of new initiatives in women's health and augments the inclusion of women, particularly minority women, into NIH-supported on-going studies. In regard to ORWH and women's health, however, the NIH institutes and centers still retain their ability to implement their own women's health research programs and activities. Like OAR, ORWH works closely with the NIH institutes and centers to assure that women's health issues become an integral part of the NIH mandate through the development and continuous refinement of an overall plan and strategy for research action. This collaboration is accomplished through the ORWH Coordinating Committee on Research on Women's Health (CCRWH) which serves as an internal advisory group to ORWH and is composed of the ICD directors or their designees; through the ORWH research and career development subcommittees; and, through the many formal and informal committees and groups convened to address the myriad issues of women's health. This consistent and continuing collaboration between ORWH and the NIH ICDs has proved fruitful in enhanced and progressive action on gaps in knowledge in women's health.

Mr. Stokes: How does the Office of Research on Women's Health identify its priorities of research and research training?

Dr. Varmus: ORWH sets priorities for its program directions in research and career development by use of intra-institute committees, advice of the ORWH Coordinating Committee on Research on Women's Health (CCRWH), interaction with the NIH staff, scientific and lay communities, and review of scientific literature. Many of the areas of interest addressing gaps in women's health research are captured in the 1991 "Report of the National Institutes of Health: Opportunities for Research on Women's Health" and form the basis for the research plan. This plan spans the spectrum of biomedical research and addresses all the ages and diversity of women. For example, ORWH provided $50,000, or about eight percent of the cost of the study, to the National Center for Nursing Research to add 150 adolescents to the original cohort for a study on "AIDS & Black Women: Testing Risk Behavior Interventions." ORWH also participates in the development and implementation of large scale studies such as the basic research RFA on "Pathophysiology of Endometriosis and Leiomyomata Uteri". This was one of the first large-scale investments for ORWH and was carried out in collaboration with the National Institute for Child Health and Human Development to stimulate new research. ORWH funded approximately 80 percent of the cost of the studies. Emerging results are now being used to guide the next iteration of studies in this area of women's health.

The ORWH is also actively involved in seeking the appropriate and sufficient representation of women in biomedical research careers. ORWH initiated a public hearing and a workshop in June, 1992 to identify barriers and issues facing women, especially minority women, in scientific careers. As a result, ORWH and the Office of Extramural Research announced a pilot program to encourage fully trained women and men to reenter an active research career after an hiatus for family responsibilities. To date, 15 women scientists have joined senior mentors at US scientific institutions to revitalize dormant careers. Approximately $1.8 million has been directed to this program. The reentry program has now evolved into an NIH-wide program with 15 NIH institutes and centers participating. In addition, ORWH has a similar program similar for intramural scientists to enter labs at NIH. To date, two scientists, (1 Hispanic) have been placed, with two more applicants being considered.

ORWH also actively collaborates with NIH institutes and centers to support activities directed toward scientific education for precollege students, especially minorities.

Mr. Stokes: When the Office of Research on Women's Health provides funds to the NIH Institutes, Centers and Divisions, do these funds typically augment existing women's programs or efforts, or do they replace funds previously provided by the Institutes, Centers, and Divisions?

Dr. Varmus: ORWH makes it clear that these funds are to augment either new or on-going research studies directed specifically to increase the number of women, especially minority women; to support new or innovative methods of recruiting or retaining women in studies; or, to initiate efforts in emerging or previously under-funded areas of research. ORWH has underscored that these awards are to expand and not to replace existing funds. In the very rare instance where problems or errors have occurred, ORWH has been immediately in touch with the institute or center and they have readily taken corrective measures.

ORWH is prohibited from directly funding any investigator or institution and therefore must make awards through the NIH institutes and centers. Because of the scope of women's health, across the life span and across all racial and ethnic groups, ORWH contributes a significant proportion of its budget to the NIH institutes and centers to augment awards, e.g., to stimulate action and to assure integration of women's health within the scientific portfolio of each. This process is particularly important to the full implementation of women's health research throughout the NIH.

Mr. Stokes: When the Institutes, Centers and Divisions are developing new women's health initiatives, do they seek advice from the Office of Research on Women's Health, elaborate.

Dr. Varmus: Initially, many Institutes and Centers sought consultation. ORWH continues to provide advice and actively participates in research development as well as planning conferences sponsored by the NIH institutes and centers. Furthermore, ORWH not only supplements a myriad of women's health studies--from those in genetics and reproductive biology to aging--but continues important trans-NIH activities in such areas as hysterectomy and DES-affected mothers and offspring. ORWH has also initiated new and targeted trans-NIH action in several key areas including autoimmune and urological diseases, reproductive health and sexually transmitted diseases, as well as occupational diseases and disabilities. ORWH has been actively seeking to institutionalize its mandate since its inception in late 1990. As such, with women's health research action increasingly embedded in the NIH portfolio and approaching similar status throughout the scientific community, many institutes and centers have now chosen to implement programs and initiatives and inform ORWH by inviting the office to consult or join in a project, conference, or particular action. The office believes that such proactive action should be supported and encouraged, for women's health, like men's health, must be an integral part of the biomedical scientific infrastructure.

BENEFITS OF NIH SUPPORTED CLINICAL TRIALS

Mr. Stokes: The budget request includes $1,178,167,000 for clinical trials. Would you please comment on the economic benefits and the life saving benefits of some of the major NIH supported clinical trials?

Dr. Varmus: Over the past eight years the NIH has identified 34 examples of clinical trials and applied research studies that have resulted in economic savings; savings that have included treatment costs and reductions in lost productivity due to morbidity and premature death. Together, the examples yield an estimated "annual" potential savings in the range $9.3 billion to $13.5 billion depending on assumptions regarding the number of new patients, the efficacy and the per-patient costs of treatment. Several of the clinical trial results are summarized below along with the corresponding estimates of one-year savings (in millions of dollars).

Close to 900 newborns saved annually from a lifetime of arrested physical and mental development through development of a mass screening device for neonatal hypothyroidism. [$193.0 - $436.2]

Development of laser-based photocoagulation treatment for early stage diabetic retinopathy which can arrest what would become impaired vision and even blindness at a later stage. [$1,184 - $1,579]

Development of measures for the prevention of the recurrence of kidney stones among the estimated 198,000 patients susceptible to such a condition. [$436.2 - $872.4]

Validation of the advantages of outpatient breast biopsies has made possible a two-stage breast cancer diagnosis/treatment procedure that provides an alternative for more than 490,000 women annually who would otherwise suffer the anguish and uncertainty of combined diagnosis and treatment under general anesthesia. [$263.2 - $526.5]

The Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that treatment of survivors of myocardial infarctions with anti-arrhythmic drug therapy to suppress asymptomatic or mildly symptomatic ventricular arrhythmias was ineffective and potentially dangerous. [$78.1 - $104.2]

Demonstration that screening and medication for isolated systolic hypertension of the elderly results in significantly fewer strokes and cardiovascular events including heart attacks. [$29.1 - $48.5]

Development of a therapy which eradicates the bacterium (Helicobacter pylori) that causes chronic gastritis and duodenal ulcers. The therapy cures individual lesions and prevents the customary life-long recurrence of peptic ulcers. [$612.2 - $816.2]

Development of cisplatin in combination therapy for treatment of advanced stage testicular cancer has provided new hope for victims of this disease. Testicular cancer is the most common malignancy in 15-35 year old males and is the most frequent cause of cancer-related deaths in this age group. The new treatment not only significantly increases the survival rate but reduces work days lost to premature mortality and morbidity. [$134.0 - $178.7]

Development of adjuvant therapy with levamisole and 5-fluorouracil (5-FU) for Dukes' C Colon Cancer. This new treatment significantly delays tumor recurrence and reduces patient risk of dying of recurrent colon cancer by one-third. Over 22,000 patients are diagnosed with this condition annually. [$161.4 - $215.2]

Development of an improved vaccine for the prevention of Haemophilus influenza type b (Hib) disease in the 2 month to 5 year age group. Hib is the leading cause of bacterial meningitis in the United States. Prevention of meningitis also protects children from a variety of neurological sequelae, including hearing loss, vision impairment, mental retardation and seizure disorders. [$137.5 - $183.3]

Development of an antiviral therapy using Acyclovir for newborn infants suffering from Neonatal Herpes Simplex. Early diagnosis and treatment can significantly reduce premature mortality and severe neurological impairment. [$137.5 - $183.3]
Development of a combined treatment with prednisone and cyclophosphamide for patients suffering kidney disease resulting from lupus has been found to sustain life-supporting renal functions longer than did the use of prednisone alone. This provides hope for the more than 1,000 persons who are afflicted with this disorder each year. [$89.8 - $119.7]

RECRUITMENT OF MINORITIES IN CLINICAL TRIALS

Mr. Stokes: To what extent has the NIH increased the number of minorities participating in its clinical trials? What progress is being made?

Dr. Varmus: In October 1992, the NIH implemented reporting requirements for awardees to report annually on the inclusion of women, and men by racial/ethnic groups in clinical trials. This information is submitted to the funding components of the NIH. To illustrate, we provide the minorities enrollment data from the AIDS Clinical Trial Group (ACTG) and from the Community Programs for Clinical Research on AIDS (CPCRA). The inclusion of minorities in ACTG has increased steadily since the formation of the ACTG in 1988. In 1993, 35% of the adult patients enrolled were of a minority group -- 20.2% Black; 12.7% Hispanic/Latino; and 2.1% other. The enrollment data for CPCRA are as follows; 41.7% Whites; 39.3% Blacks; 17.1% Hispanic/Latino; 0.6% Asian/Pacific Islander; 0.4% Aleut Eskimo/American Indian; and 0.9% others.

NIH staff have participated in numerous activities to inform and educate the public of the 1993 Guidelines. In addition, we plan to publish the "Outreach Notebook on the Inclusion of Women and Minorities in Biomedical and Behavioral Research" in June. This notebook should assist researchers in the recruitment and retention of women and minorities in clinical trials. We have made significant progress toward an increased awareness among researchers of the need to include women and minorities and their subpopulations in clinical research.

HISTORY OF MINORITY SUPPLEMENTS

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Varmus: Since the NIH program of Research Supplements for Underrepresented Minorities was developed in fiscal year 1990, the NIH has made more than 2,500 awards. This program provides support for individuals at the high school, college, graduate, postdoctoral, and faculty levels.

The intended purpose of this program is to attract and encourage minority individuals to enter and pursue biomedical and behavioral research careers in areas within the missions of all the awarding components of NIH. Although we will be very pleased if individuals supported by the supplement program proceed to independence as an investigator, our primary goal is to increase the racial and ethnic diversity of researchers engaged in biomedical research at all career levels.

Because the minority supplement program is only in its fourth year, most of the individuals supported will still be in the training phases of their careers. Also, examining the outcome of the program by looking only at those who become Principal Investigators on NIH research grants will provide a very narrow and extremely stringent assessment of quality. Nevertheless, some of the more senior recipients of minority supplements may have had an opportunity to apply for and receive an NIH grant award. Over the next few weeks we will match our records on recipients of minority supplements with records of individuals receiving research grants to see if there are any overlap.

HIGH PERFORMANCE COMPUTING INITIATIVES

Mr. Stokes: The FY 1995 budget request includes $81.8 million, or a $24 million increase, for high performance computing. How will the nation benefit from this investment? In the development of networks to medical schools, to what extent will historically black medical schools be involved?

Dr. Varmus: The application of information technologies derived from the HPCC program has the potential to significantly improve health care delivery. There are two kinds of information which every health care professional needs: knowledge of the scientific basis of health and disease, as represented in the published medical literature and in scientific databanks; and patient-specific information, such as laboratory test results, x-rays, and the record of previous findings and prior medical care. Though we have systems such as MEDLINE which permit searching of the medical literature within minutes nationwide, most of the information sources for health care are embarrassingly primitive. The majority of records of medical care are hand written paper records with a high likelihood of being lost or misplaced. Patients who see several providers usually have several fragmentary records in the offices of each of those providers. Though there are laboratory computer systems and radiology computer systems and administrative computer systems in hospitals and clinics, they are usually joined only by paper printouts. In the age of advanced information technologies in which we live, this is nothing short of a national disgrace, and is itself a risk to the health of every citizen.

The HPCC program will support research and development of solutions to these problems: integrated information systems which incorporate both scientific and patient-specific clinical information, and make it available to health professionals in a distance-independent electronic form over high speed networks, while protecting security and privacy. In FY 1993 and FY 1994, NLM made competitive research contract awards for testbed networks for linking hospitals, clinics, doctor's offices, medical schools, medical libraries, and universities to enable health care providers and researchers to share medical data and imagery. A variety of rural and urban projects were funded in West Virginia, Pennsylvania, Indiana, Illinois, Iowa, Kansas, Oregon, and California. These projects will create and evaluate advanced methods for managing health care information, and provide models and standards for deployment of such systems nationwide.

NLM has been collaborating with the National Science Foundation and the National Network of Libraries of Medicine to help health care institutions, including Historically Black Medical Schools connect to the Internet. Morehouse was one or our earliest awardees, receiving one of the ten grants made in the first year of the program in 1992. Three of the other grants awarded were to institutions serving primarily inner city populations. When we next announce the program we intend to emphasize our interest in applications from health units which play an important role in health care delivery to inner city or rural populations.

Additionally, an outreach initiative by NLM's Toxicology Information Program is aimed at strengthening the capacity of nine Historically Black Colleges and Universities to train medical and other health professionals in the use of toxicological, environmental, and occupational information resources provided by NLM. In cooperation with the Agency for Toxic Substances and Disease Registry, training and online access have been provided for 27 additional HBCUs with programs and concerns in the environmental and hazardous waste areas.

RESEARCH PARTICIPATION OF HBCUs

Mr. Stokes: What are some of the major initiatives underway at the NIH to increase the participation of Historically Black Colleges and Universities in biomedical research?

Dr. Varmus: The NIH has developed a two-pronged strategy for increasing the participation of Historically Black Colleges and Universities (HBCUs) in biomedical research. This comprehensive strategy is being coordinated by the Office of Research on Minority Health (ORMH) in collaboration with the Institutes.

The first prong involves the development of new pilot programs and the expansion of existing program activities which focus primarily on minority institutions and minority investigators. These initiatives includes such programs as: Minority Access to Research Careers (MARC) Program; Minority Biomedical Research Support (MBRS) Program; Research Centers in Minority Institutions (RCMI) Program; Minority High School Student Research Apprenticeship Program (MHSSRAP); Minority International Research Training Program.

These programs provide funding to strengthen research capabilities of minority institutions and to increase the participation in biomedical research of faculty and students from high schools, two- and four-year colleges and universities, and health professional schools.

The second prong of the strategy addresses the need to strengthen the ability of HBCUs to participate in the NIH competitive grant awards process. This facet is significant because the majority of the research sponsored by the NIH is supported through this process. The NIH strategy includes three initiatives in this regard:

Technical Assistance Workshop. These workshops provide opportunities for Institutes to work with the Office of Research on Minority Health to increase the grant writing capabilities of HBCUs and, thus, increase their success in applying for NIH grants.

Institutional Research Supplements Program. This program is designed to foster meaningful collaboration between minority and majority institutions. As a result of such collaboration, majority institutions will be assisted in their efforts to recruit minorities into clinical trials and minority institutions will better understand the resources and expertise needed to conduct biomedical research.

Research Supplements for Underrepresented Minorities Program. Under this program, administrative supplements to NIH supported grants are provided for the purpose of attracting minority faculty and students into the field of biomedical research. Experience gained through research opportunities with seasoned scientists will enable minority students and scientists to develop skills needed to successfully compete for NIH grants as well as to appropriately manage them.

Each of these efforts will promote the competitiveness and thus the success rate of HBCUs in competing for all NIH-sponsored research grants.

INTRAMURAL REVIEW TASK FORCE

Mr. Stokes: In a recent draft letter to the Chairman, the Department indicated that the report is being revised to incorporate modifications to the recommendations of the task force on the status of the intramural minority scientists. What was the task force's charge?

Dr. Varmus: The charge to the Committee on the Status of Intramural Minority Scientists was "to examine the status of underrepresented minorities in the Intramural Research Program of NIH...to provide a comprehensive view of the issues inherent in the recruitment and retention of minorities."

Mr. Stokes: What are the major recommendations of the intramural minority scientists task force?

Dr. Varmus: The recommendations of this committee are summarized in the attached document, "Status of Intramural Minority Scientists."

Mr. Stokes: Will these recommendations be implemented? What is the timetable for implementation, and how will implementation oversight be monitored?

Dr. Varmus: Recommendations of the committee, as indicated in this document, will be implemented during the next calendar year.

Mr. Stokes: Did the task force include individuals from outside of the NIH? Explain.

Dr. Varmus: No. The committee was comprised of tenured and non-tenured intramural scientists and administrative professionals from NIH's Offices of Education and Equal Opportunity, as well as EEO officers from various Institutes, Centers and Divisions of NIH. Responsibility for oversight of implementation of the committee's recommendations is in the Office of the Director.

REPRESENTATION OF MINORITIES AT GS-15 AND ABOVE

Mr. Stokes: At the NIH overall, currently, how many African Americans are at the GS-15 and above level? In what positions are they? How many GS-15 and above positions are there at the NIH? How many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem at the NIH?

Dr. Varmus: The NIH currently employs 50 African Americans at Grade 15 or above (37 Grade 15; 8 SES; 5 PHS Corps O-6); a total of 1,189 positions at the NIH are currently filled at Grade 15 and above. African Americans in these grades hold a variety of positions, such as Supervisory Contract Specialist (Chief of the Contracts Branch of a major organization); Supervisory Health Scientist Administrator (Deputy Branch Chief in a major extramural program component); Physicians and Supervisory Physicians; Supervisory Biomedical Engineer; Chief of a major extramural program in one of the largest Institutes; Deputy Executive Officer of a major research Institute; and Directors of large administrative programs.

The NIH, as with all PHS Agencies, has been under two freezes. The first prohibits promotions or outside appointments to GS-14 or above, the second prohibits all hiring from outside the PHS. Exceptions may be granted by the Assistant Secretary for Health. Since the imposition of these freezes, the NIH has submitted 10 exception requests for promotions of NIH employees to GS-14, including three African American employees. We have also submitted six exception requests to hire individuals from the outside at Grade 14 or above, including 3 African Americans. We understand that these exception requests have been approved, and we are awaiting final authorization on each case. We also have had blanket exception requests to hire students under our summer and Stay-in-School programs approved. These programs typically employ a high percentage of minority individuals (our Stay-in-School Program is approximately 80 percent minority -- primarily African American).

We understand that additional exceptions may be approved very soon, but do not know when the hiring freeze will be lifted. The freeze on promotions or outside hiring at the senior grades resulted from an Executive Order to reduce senior level positions by at least 10 percent of the overall FTE reductions. It is likely that this freeze will continue until the NIH is able to meet its reductions in these senior level grades.

COST OF CLINICAL CENTER REVIEW

Mr. Stokes: The FY 1995 budget request includes $2.5 million for the Clinical Center Review Project. Is this the total cost of the Review Project or is each of the Institutes, Centers, and Divisions with intramural programs going to be tapped for this project as well?

Dr. Varmus: It is believed that the $2.5 million is sufficient to review and analyze the various options for the renewal of the Clinical Center as necessary to support and facilitate a final decision on its future. Additional funds will be required to begin planning and design of the selected option. It is not anticipated at this time that the Institutes, Centers, and Divisions (ICDs) will be tapped for funding of this review.

CLINICAL CENTER COMPLEX

Mr. Stokes: When does the NIH expect to make a decision regarding the future configuration of the Clinical Center complex? To what extent has the NIH considered using the mortgage approach to fund the construction or renovation effort?

Dr. Varmus: The NIH is currently reevaluating and developing various Clinical Center renewal options in view of the External Advisory Committee review of the NIH Intramural Research Program. A decision on the approach for the Clinical Center renewal will be made following the Committee's final report and a review and analysis of the Committee's recommendations for the Intramural Program and its impact on the various facility options. A recommended facility approach needed for the renewal of the Clinical Center is anticipated within 6 to 9 months.

The NIH is currently investigating alternative funding approaches such as the extended financing (mortgage approach) and the possibility of requesting a constant level of funding each year to stabilize the budgetary requirements.

WILLIAM H. NATCHER BUILDING

Mr. Stokes: How far away is the completion of the construction of the William H. Natcher Building? Will the new facility be large enough to house all NIH staff that are currently utilizing off-campus sites?

Dr. Varmus: The William H. Natcher Building is being constructed in two separate phases. Phase I contains an office building component and a conference center component that are currently under construction. Schedules are as follows:

The Phase I office building construction is currently scheduled to be completed in August 1994. Preparation for the actual occupant move-in, such as establishment of the local area networks and delivery of new ICD provided furniture, is ongoing and installation will begin at that time.

The actual occupancy by the ICDs will begin in October 1994 and be completed in December 1994.

The Phase I conference center construction will also be completed in August and fit-out of equipment will begin at that time. The conference center will be available for use in January 1995.

The solicitation for procurement of Phase II construction has been deferred until the NIH Campus Plan is approved by the National Capital Planning Commission (NCPC), estimated for September 1994.

Currently, the Phase II occupancy is scheduled to begin in April 1998 provided NIH receives NCPC approval of the NIH Campus Plan in September 1994, NCPC approval of the Natcher Phase II design in November 1994, and the remaining funds are received in FY 1995 and FY 1996.

Even upon completion of Phases I and II of the Natcher Building complex, there will still be approximately 2,500 staff located in locally leased facilities.

FTE FREEZE AT NIH

Mr. Stokes: Has the NIH requested relief from the freeze? If so, what was the response?

Dr. Varmus: The NIH requested relief from the Public Health Service (PHS) hiring freeze imposed in December 1993 because NIH had successfully managed its FTE ceiling. The request is under consideration by the PHS.

AIDS RESEARCH IN WOMEN, CHILDREN AND YOUTH

Ms. Lowey: I am aware of a new initiative between the NIH and the Maternal and Child Health Bureau that coordinates research and care using Title IV Ryan White Care Act funds for care and NIH research funds for clinical research. This initiative is called the Adolescent Medicine HIV/AIDS Research Network and is examining concerns about enrolling youth in clinical trials and other research programs. The initiative is aimed at answering questions about whether the course of HIV disease is different in adolescents as compared with adults.

Could you explain to the Committee how the new consolidated budget for AIDS research will impact AIDS research priorities in areas of pediatric, youth, and women's issues and this new initiative?

Dr. Varmus: The consolidated budget for AIDS research will provide the opportunity to highlight important areas of AIDS research related to children, adolescents and women. The planning process will provide the basis for identifying such areas of high priority through consensus of the research community and advocates with expertise in these areas. This initiative is an excellent example of a program of cross-cutting research that is also linked with access to care and will remain a high priority under the new budget process.

CONSOLIDATION OF AIDS RESEARCH PORTFOLIO

Ms. Lowey: How will the consolidated research budget for AIDS improve the planning and management of this formidable portfolio?

Dr. Varmus: The consolidated research budget for AIDS will improve the planning of AIDS research through an ongoing planning process that will include significant input from the research and HIV/AIDS advocate community in the development of consensus concerning research priorities independent of ICD missions. Management of the budget will be achieved through reallocating funds to the ICDs for projects that are specifically tied to the AIDS research plan developed through the planning process described, thus ensuring that research projects are related to the identified research priorities.

HIGH PERFORMANCE COMPUTING

Ms. Lowey: What is the basis for such a large increase in the area of high performance computing? How will high performance computing expedite the development of clinical applications from basic research? What are the principal barriers to improving linkages between hospitals, clinics, academic health centers and other important health providers?

academic health centers and other important health providers?

Dr. Varmus: NLM's HPCC Broad Agency announcement experience illustrates the opportunity provided by new computing and communications technologies for health care. In FY 1993 there were 136 applications for support, of which 85 were found to be worthy of support by peer review, and 53 were highly meritorious. Support for these 53 applications would have required $150.8 million; resource constraints led NLM to fund 12 projects worth $27 million over three years, including testbed networks (citywide, statewide and national), virtual reality experiments, telemedicine (both statewide and discipline-based systems), and information access (linking images to patient records). Clearly, there is much work to be done and many technically competent and innovative organizations eager to do the research and development for national information infrastructure applications in healthcare. No single, monolithic model for computer usage or data communications will suffice for the nation's remarkably heterogeneous enterprise of health care delivery; a number of demonstration projects and prototype systems for various demographic and technical scenarios will need support. NLM would use competitive research contracts and grants to direct the increase in HPCC funding to the most creative and talented academic and commercial R&D projects nationwide--those with the potential to make a real and substantial impact on the improvement of health care throughout the country.

Thanks to the sustained investment in basic research and technology development by several of the federal agencies with HPCC programs (primarily ARPA, DOE, NASA and NSF), there have been developed fundamentally new computer designs and very high speed digital networking technologies. The focus of the NIH HPCC projects is to apply these advanced tools to biomedical challenges, ranging from the understanding of human health and disease on a molecular level, to the efficient delivery of health care. High performance computing and communications expedite the development of clinical applications from basic research in a number of ways. For example, massively parallel computers enable the design of new drugs based on the structure of target molecules, leading to creation and testing of pharmaceuticals which is faster and more efficient than the trial-and-error screening of compounds. New gene sequences are being found daily as part of the Human Genome Project, and digital networks forward these data to central databanks such as GenBank, the national DNA sequence databank at NLM's National Center for Biotechnology. Here, computerized analysis quickly determines the relationship of newly discovered genes to those already known. High speed networks allow both basic and clinical researchers to share and analyze research findings collaboratively, though they may be in laboratories thousands of miles apart. Due in part to advanced computers and networks, molecular biology has become a "24 hour" science where a gene sequence can be cloned, sequenced, and analyzed computationally in a day or less; this remarkable capability has generated new diagnostic probes for cystic fibrosis, Huntington's disease, and created prototype diagnostics for several common cancers. These trends to shortening the time lag between the discovery of new knowledge and its effective application to reduce human disease and suffering will accelerate as new information technologies are deployed in both research laboratories and clinics.

There are a number of technical, social, and legal barriers to improving the information links among health care organizations. They include:

There is the lack of agreed-on standards for information exchange. We desperately need widely accepted standards for representing and communicating medical and billing information. Our health care institutions are encumbered by proprietary "legacy" systems which cannot share data, and represent islands of automation floating on (and generating) seas of paper printout.

A related problem is that, for telemedicine systems involving licensed health professionals from different states, differing state licensure and accreditation requirements are an additional complication. It is not clear what the malpractice implications are for providers, remote from each other and remote from the sources of information on which they rely, who use telemedicine and various computerized aids in their practices.

Privacy and confidentiality of computerized records is an essential requirement. How do we balance the need to protect an individual's electronic medical record, yet make it instantly available for emergency treatment purposes anywhere that it is needed? Much of the technology created in the defense and intelligence communities, and financial systems, can and will be incorporated into telemedicine systems that are widely deployed. User authentication, data encryption, and other technologies are important components of the High Performance Computing and Communications initiative that will be incorporated into future medical systems.

A substantial barrier is lack of knowledge on how the costs of telemedicine compare with the benefits to be gained. To assume that large savings would automatically accrue would be foolhardy. An important role for the Federal Government is to investigate the potential savings to society by applying telecommunications and other High Performance Computing and Communications technology to health care. There is an evaluation component in the recent telemedicine awards from NLM, and a continued emphasis on critical evaluation of the costs and benefits of healthcare information networks is needed.

SUPPORT FOR BIOETHICS IN HUMAN GENOME RESEARCH

Ms. Lowey: You testified that a portion of the budget for the Human Genome Project will be devoted to the study of ethical, legal and social issues of human genome research. Can you explain more fully how the Center plans to use its appropriation in this area? Has the Center established any specific research plans with respect to these issues? How will you know if these studies are effectively addressing these most important concerns?

Dr. Varmus: The National Center for Human Genome Research (NCHGR) will continue to devote at least 5 percent of its budget to support a three-pronged program of research, education, and policy analysis addressing the ethical, legal and social implications of new advances in human genetics.

The research program supports competitively-awarded studies conducted by investigators from all around the United States. Over 50 different projects have been funded since 1990. The goal of this research is to establish the body of knowledge needed in order to develop sound policy options in this area. This research program is conducted jointly with the U.S. Department of Energy and many projects are co-funded by other NIH institutes.

For example, this year the ELSI Branch undertook a new initiative (in conjunction with the National Cancer Institute, the National Institute of Nursing Research, and the National Institute of Mental Health) to examine the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer, and to gather information needed to establish clinical protocols for the optimum use of these risk assessment technologies.

The education program at the NCHGR consists both of extramural grant support for model education projects and of the direct activities of the intramural Education Office and Medical Genetics Training Program. The goal of these activities is to prepare health care professionals, teachers, and the U.S. public to use the information provided by new advances in genetics effectively and responsibly.

The Human Genome Project's policy analysis efforts in this area are conducted by the NIH-DOE Joint ELSI Working Group; an interdisciplinary panel of relevant experts which is charged with monitoring the research being supported and articulating the policy options that emerge for both professional practice and public policy. One example of that Group's work is their report on Genetic Information and Health Insurance, released in May, 1993, which has become influential in helping illuminate the impact of genetic advances on health care coverage and reform. In FY 1995 the Group's activities have been reorganized to focus on specific tasks that need urgent attention: genetic privacy, genetics and health care reform and the regulation of commercial genetic testing. Task forces of Working Group members and outside experts have now been established for each of these areas and an executive committee appointed to oversee the process.

The specific research plans and policy analysis goals for the Human Genome Project's ELSI efforts were initially spelled out in the first Five Year Plan for the Human Genome Project in 1990. Four high priority areas were identified: 1) the responsible integration of new genetic tests (such as cancer risk assessments) into clinical practice; 2) improving protections on the privacy of personal genetic information; 3) ensuring fairness in the use of genetic information by insurers, employers, and other social institutions; and 4) improving public and professional understanding of new advances in genetics. In 1994, these plans were amplified by the second five year plan for the Human Genome Project.

There are several indirect measures that will be useful in assessing the success of the Human Genome Project's efforts to address the ethical, legal and social implications of new advances in genetics: 1) the creation of sound, well informed, public and professional policies; 2) the improvement of professional and public understanding of genetics issues; 3) the sophistication and balance of media presentations; and 4) the establishment of a healthy research community studying the issues.

Since FY 1990 progress has occurred as measured by all these criteria, but we expect even more important results, now that this novel and path-breaking program is well-established and initial efforts mature.

TECHNOLOGICAL ADVANCES AND COST OF HUMAN GENOME PROJECT

Ms. Lowey: Aren't the cost estimates for the Human Genome Project based on significant improvements in the efficiency of the mapping process? Is it appropriate to base budget estimates on assumed technological advancements? How confident are you in our capacity for making the technological advancements necessary to sustain the budget?

Dr. Varmus: As you have noted, the initial planning for the Human Genome Project, as reflected in documents such as the 1988 National Research Council report and the 1990 NIH-DOE plan, clearly recognized that the goals laid out for the Human Genome Project were extremely ambitious and that realization of those goals would require significant technological advances in all areas. As the genome project has proceeded, progress along a broad range of technological fronts has, in fact, been impressive. Several examples can be offered: new types of genetic markers that have made genetic mapping much more efficient; new strategies for assembling physical maps that have enabled development of those maps to proceed as rapidly as envisioned; the improvement of first-generation automated instruments for large-scale DNA sequencing and the development of new robots and other automated instruments for all stages of genome research. The Human Genome Project has been successful in attracting the interest of engineers and scientists from disciplines that have traditionally not participated in biomedical research. The participation of such individuals is essential to achieve the needed technological advances.

Despite this progress, attainment of the ultimate goals of the Human Genome Project remains a challenging task. Further substantial improvements in technology are needed in all areas, but particularly in DNA sequencing, if these goals are to be reached and if the fruits of genome research are to become readily available to the public. Given the progress we have made so far, I am confident that the goals of the Human Genome Project can be reached within the budget originally projected.

NIH OVERSIGHT OF CLINICAL TRIALS

Ms. Lowey: In reviewing the chain of events that led to the use of falsified data in the breast cancer study headed up by Dr. Fisher at the University of Pittsburgh, a number of experts have cited the failure to conduct the required on-site audits of patient records as an important reason why the fraud was not uncovered early on in the study. Is the NIH considering any changes in its procedures to ensure that on-site audits of patient files take place when required?

Dr. Varmus: The fraud was uncovered by an audit of the case reports to the National Surgical Adjuvant Breast and Bowel Project (NSABP) coordinating center at the University of Pittsburgh. The investigation was initiated by the University of Pittsburgh and then by the Public Health Service Office of Research Integrity. It was determined that fraud had occurred, and the investigator in Canada was sanctioned. The University of Pittsburgh was directed by the National Cancer Institute (NCI) to make the findings public. The NSABP had determined that the fraudulent data did not alter the final conclusions of the study and they did not act expeditiously. The National Cancer Institute has acknowledged that the NCI did not pursue publication of the fraudulent data as vigorously as they should have. However, the NCI has already initiated organizational and procedural changes to assure that this will not happen again. They have established a special branch to assure adherence to protocols in all NCI-supported clinical trials. The NIH is currently reviewing policies across all the component institutes and centers on audit and follow-up on clinical trials. Policies will be put in place as needed to avoid such problems in the future.

RESOLUTION OF EMPLOYEE COMPLAINTS AGAINST NIH

Ms. Lowey: Considering that NIH recently lost the Jensvold case in federal district court, in which the plaintiff was judged to have suffered from discrimination, retaliation and damage to her professional reputation during her time at NIH, I would be interested to learn whether you will revise the apparent policy of fighting many of these discrimination complaints in court. Or do you plan to take steps to get the NIH to settle out-of-court, and resolve the outstanding complaints?

Dr. Varmus: The NIH position will be made on a case by case basis, dependent upon the merits of the case. We are willing to consider alternative methods for resolution of complaints. However, final decisions are made by the Department of Justice.

SEXUAL HARASSMENT/DISCRIMINATION AT NIH

Ms. Lowey: What policies and procedures are being implemented at NIH to create a more positive working environment for women scientists, and reduce the number of harassment and discrimination complaints that are being filed with the Equal Employment Opportunity Commission (EEOC)? Do you have a timeline for implementation of any such policies?

Dr. Varmus: The NIH Task Force on the Status of Intramural Women Scientists was established in 1992 and continues to develop recommendations to improve the work environment. The goal is to have the Task Force recommendations implemented by the end of Fiscal Year 1994.

The following actions have already been taken: A Trans-NIH Committee of Women Scientists was formed to function as advisors to the Institute Scientific Director (SD) and act as a channel for communication between the SD and the women scientists within their Institute.

Each SD has been charged with meeting with his woman scientist advisor to examine the data on salary compensation to insure it is free of gender bias.

The visibility of intramural women scientists of all racial and ethnic groups is being increased by including them in greater numbers at NIH forums, seminar series and grand rounds at NIH-sponsored meetings.

The process of recruitment for tenure track positions at the NIH has been completely revised to require nationwide searches for all new positions; search committees must contain minority and women representatives; a new NIH Tenure Review Committee, including minority and women scientists, will be established to advise on tenure decisions.

TRAUMA RESEARCH

Mr. Serrano: Can you give us a progress report on the work of the Trauma Research Task Force.

Dr. Varmus: The National Institutes of Health Revitalization Act of 1993 directed NIH to establish "a comprehensive program of conducting basic and clinical research on trauma." Specifically, the language called for two major actions required to implement this legislation: (1) the establishment of a committee to coordinate trauma research; and (2) the development of a plan to carry out the activities of the Program.

In response to the first directive, the NIH established an NIH Trauma Research Coordinating Committee composed of the Directors of each of the relevant Institutes, Centers, and Divisions of NIH. The Committee will serve to (1) provide a forum for the exchange of information and views; (2) strengthen and improve reporting on research and related activities in trauma; and (3) provide a focus and central point of contact for the NIH in interactions with other Federal agencies and outside organizations.

In response to the second directive, the NIH established a Trauma Research Task Force composed of members of the extramural scientific community who are expert in the fields of basic and clinical research related to trauma care. The Task Force held a comprehensive meeting, from January 31 through February 2, 1994 to initiate the development of a plan for trauma research that will identify promising research opportunities; establish priorities among competing demands for resources; and chart the future course of trauma research for the next decade, and beyond. The multidisciplinary nature of the Task Force, which included trauma surgeons, epidemiologists, psychologists, and rehabilitation professionals, reflects the complexity of the scientific base necessary to examine the issues and underpinnings of trauma research. At the meeting, emphasis was given to basic and clinical research along the continuum of trauma care. Other important issues included trauma care needs of special populations such as children, the elderly, minorities, and women; and injury prevention on primary, secondary, and tertiary levels. Drafting of the plan is in progress, and a copy of the final plan will be provided by July 1, 1994 to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate.

Mr. Serrano: It does not appear that prevention of injury is an area the legislation requires NIH to address. Is the Task Force likely to propose including research in the Plan?

Dr. Varmus: You are correct, prevention of injury was not an area the legislation requires the NIH to address. Specifically, the legislation required that the NIH program include studies with respect to all phases of trauma care. This would include: pre-hospital evaluation; resuscitation; surgical intervention; critical care; infection control; wound healing; nutritional care; and support and medical rehabilitation.

However, the Task Force has proposed the inclusion of prevention research in the plan. The Co-Chairpersons, Dr. Howard Champion and Dr. Dorothy Gordon, as well as many of the members of the Task Force are involved in the programs of CDC's Center of Injury Control and Epidemiology as they relate to trauma. Many of the Task Force members were also involved in the drafting of another DHHS plan entitled, "The Draft Model Trauma Care System Plan." Within this plan, regional trauma centers are charged with the development and institution of injury prevention programs which include public education and the provision of passive protective devises such as air bags and smoke alarms. The Task Force is very cognizant of the impact of preventative strategies and considers prevention of trauma a high priority.

Consequently, prevention will continue to be a major part of a coordinated PHS effort, is an agenda item for the NIH Trauma Research Coordinating Committee and is encouraged by the draft NIH Trauma Research Task Force Report.

Mr. Serrano: As far as you know, is the Task Force working with other Public Health Service and other Federal entities that are involved in trauma-related research and other activities such as the CDC or the National Highway Traffic Safety Administration to set a trauma research agenda that will be useful to them.

Dr. Varmus: The NIH Task Force has included representatives from other agencies in their deliberations. Representatives from other PHS agencies were invited to serve as resource people to the non-government experts. The Task Force also included Federal scientific expertise among its membership. For example, Dr. Basil A. Pruitt from the U.S. Army Institute of Surgical Research, a leading trauma care researcher and clinician was the co-chair of the Infection/Sepsis/Nutrition Panel. In addition, the NIH plans to share the draft report, for input, as well as the final task force report, for implementation, with the National Highway Traffic Safety Administration, CDC's Center for Injury Control and Epidemiology and the Agency for Health Policy Research. An important recommendation by the Task Force is that there be enhanced coordination and collaboration between and among Federal agencies.

The NIH Trauma Research Coordinating Committee will also invite representatives of other Federal agencies to give presentations and participate in its deliberations resulting in a trauma research agenda that will be useful to all Federal agencies.

RECRUITMENT OF FUTURE SCIENTISTS IN BIOMEDICAL RESEARCH

Ms. Delauro: I am concerned about the training of new research scientists. I frequently hear from researchers that we are in jeopardy of losing the next generation of promising young research scientists we will need in the coming decades to other fields. Could you share with the Committee what factors you believe are hurting our efforts to attract new scientists and what specific steps you will take to make sure we recruit and retain our future biomedical researchers?

Dr. Varmus: We too are very concerned about our ability to attract the brightest young scientists into biomedical research careers. Several factors have been identified by the National Academy of Science which are thought to discourage students from considering a career in research. These factors include the perception that funding for research is uncertain and difficult, that salaries for researchers are too low, that the period of training is long and arduous, that graduates of medical and graduate schools often have substantial educational debt burdens, and that training stipends are too low.

Many of these problems can be addressed by the NIH while others cannot. In fiscal year 1994, for example, we raised stipends for graduate students and entry level postdoctoral trainees, recognizing that our current graduate stipend of $10,000 is still lower than all other comparable Federal research training programs and must be increased further in order to compete for the best students. We have also tried to address the perception that research funding is difficult to obtain by offering First Independent Research Support and Transition (FIRST) awards and small grants which selectively supports individuals who haven't previously been supported by the NIH. Also the success rate is highest for the youngest applicants. Most of the NIH institutes offer more generous paylines to investigators applying for FIRST awards. Also, the NIH has reduced the average award period on research grants over the last several years to increase funds available for new and competing awards. Finally, the NIH has been discussing a system of streamlined career awards that will help individuals make the transition from training to independence. The period of training will remain long and arduous and many trainees will continue to choose between clinical careers and careers in research. We can hope to improve the attractiveness of a career in research by offering competitive stipends and reasonable opportunities to launch an independent career.

RECRUITMENT AND RETENTION OF WOMEN AND MINORITIES

Ms. Delauro: Could you also tell the Committee what specific steps you are--or will be--taking to enhance the recruitment and retention of women and minorities? Do you have specific goals you would like to achieve?

Dr. Varmus: We continue to worry about the diversity of the research laborforce and the recruitment of underrepresented minorities and women. We have a number of special training programs for minorities that recruit at the college level. These programs include the Minority Access to Research Careers (MARC) Honors Undergraduate Program, the Minority Biomedical Research Support (MBRS). We also have programs that bridge between community colleges and four year institutions and between masters degree programs and doctoral level programs. We support minority graduate fellowships, minority supplements to research grants, and we have developed a policy that requires all training program directors to actively recruit minorities into their training program. In addition, NIH is in the process of implementing two new programs authorized in the NIH Revitalization Act of 1993 targeted to individuals from disadvantaged backgrounds--the Undergraduate Scholarship Program and the Loan Repayment Program.

Women still remain underrepresented in the doctoral level research laborforce, but the problem does not stem from an inability to recruit women into training. At the graduate and postdoctoral level, more than 40 percent of training positions are filled by women. In some fields, women comprise 60 percent of the training pool. Women still do not enter academic faculty positions as rapidly as men and only about 20 percent of the Principal Investigators on NIH research grants are women. To attempt to improve recruitment at levels beyond postdoctoral training, the NIH has recently launched a reentry programs for individuals who have left research to attend to family responsibilities but now wish to update and improve their research skills in order to restart their career as a researcher. We have changed the leave policy for our trainees and fellows to allow for a period of parental leave when it is consistent with the institutional policy. We are also planning to implement changes in our training mechanisms that will allow individuals with family care demands to train on a part time basis. We are hoping that all of these changes will improve the retention of women so that in greater numbers they can become productive biomedical and behavioral researchers.

MANAGING THE AIDS RESEARCH PORTFOLIO

Ms. Delauro: Does the management of the AIDS research portfolio present challenges that are different than the research portfolios for other serious diseases, like heart disease or cancer?

Dr. Varmus: Yes, the AIDS-related research portfolio is unique in that AIDS-research is sponsored by all of the Institutes and Centers of the National Institutes of Health (NIH) thus requiring special management. With other major diseases such as cancer and heart disease, the planning and management can be carried out by one or two institutes. Furthermore,it should be noted that more than 50 percent of the AIDS research portfolio supports basic biomedical research. The establishment of the OAR Coordinating Committees, as mandated by the NIH Revitalization Act of 1993, will provide for increased coordination and collaboration among the ICDs based on scientific opportunities. Similarly, the annual review of the NIH Plan for HIV-Related Research will provide a comprehensive plan for basic biomedical and clinical research.

HIV/AIDS research has major implications and has already benefitted other diseases. The scientific insight and expertise gained from HIV/AIDS research will continue to be utilized to resolve a wide spectrum of other basic scientific issues in the fields of virology, immunology, microbiology, molecular biology, oncology, and animal models. Similarly, many of these important advances can be directly applied to clinical medicine. HIV/AIDS research has helped establish new approaches for the design and conduct of clinical studies addressing the special recruitment requirements of women, minorities, and other underserved populations. Thus, the nation's investment in HIV-related research is providing major benefits in understanding and treating other diseases.

Basic scientific understanding resulting from AIDS-related esearch is being advanced in the following areas:

- the function of the immune system which has implications for diseases such as hepatitis, herpes, certain lymphomas and sarcomas, and autoimmune diseases including systemic lupus erythematosus;

- the mechanisms of gene expression which will further research on oncogene transformation that can result in neoplasia and cancer;

- central nervous system pathology which will further research on dementia, Alzheimer's disease, neuropsychological disorders, and multiple sclerosis;

- the transmission of sexually transmitted diseases, including hepatitis, herpes, syphilis, chlamydia, and gonorrhea, and associated behavioral factors;

- the blood-brain barrier which will further research on the mechanisms involved in passage of infectious agents across this barrier as well as passage of therapeutic agents across this barrier for treatment of various diseases such as encephalitis, and meningitis;

- the development of cardiovascular diseases will further research on pulmonary, cardiac, and rheumatic disorders resulting from various infections;

- the development of nutritional disorders will further research in such areas as wasting syndromes, metabolic abnormalities, and gastrointestinal dysfunctions;

- the development of nervous and immune systems in children will further research on neurological and neuropsychological disorders and immunological disorders including certain autoimmune disorders and cancers; and

- retroviral-associated malignancies, such as Kaposi's sarcoma, cervical dysplasia, anogenital cancers, and non-Hodgkin's lymphoma.

FUNDING FOR DISEASE PREVENTION

Ms. Delauro: How much will the NIH spend on research into disease prevention in FY 95? How does that compare to FY 94 and FY 95?

Dr. Varmus: The NIH expects to spend approximately $2.8 billion for prevention research in FY 1995 as compared to $2.7 billion in FY 1994 and $2.5 billion in FY 1993.

TUESDAY, APRIL 19, 1994.

NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

NATIONAL INSTITUTE OF DENTAL RESEARCH

Witnesses

SAMUEL BRODER, DIRECTOR, NATIONAL CANCER INSTITUTE

KENNETH OLDEN, DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

HARALD LÖE, DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH

Mr. SMITH. We have three institutes this afternoon, and perhaps we can do all three statements first. Then we will have questions. You may proceed.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Mr. Chairman, could I introduce my colleagues who are here with me today.

Dr. Samuel Broder, who is the Director of the National Cancer Institute will speak first. On my left, Dr. Kenneth Olden from the National Institute of Environmental Health Sciences, and Dr. Harald Löe, who recently announced his retirement as Director of the National Institute of Dental Research.

OPENING STATEMENT

Mr. SMITH. Go ahead.

Dr. BRODER. Mr. Chairman, thank you for the privilege of being here. This is a time of significant progress in cancer research, but it is also a time of considerable challenge. A number of cancers are on the rise, notably breast, prostate and lung cancers.

The National Cancer Institute has three foundation stones: basic research, clinical trials and a nationwide network of cancer centers that provide the support for the new discoveries needed to improve cancer prevention and cancer care in the community.

Translation of advances made at the laboratory level into clinical practice is speeded by the Specialized Programs of Research Excellence (SPORE) in breast, prostate, lung and, most recently, in gastrointestinal cancers.

Diffusion of research results to the public and professional community is carried out through the Cancer Information Service, our Physician Data Query computer network, CANCERFAX, Cancer Net and the Journal of the National Cancer Institute.

BASIC RESEARCH

There has been substantial headway in many areas of basic research. Thus, a number of genes involved in specific cancers have been identified. You have already heard Dr. Varmus discuss two genes that confer substantial risk for the development of cancer of the large bowel. Such discoveries also have a strong impact for ovarian cancer and endometrial cancer. This is a concept that we will return to frequently, the concept that shedding light on a variety of diseases is possible through a fundamental program of basic research.

GENETIC DISCOVERIES

Each new genetic discovery guides the development of specific diagnostic approaches, interventions and treatments. For example, a new gene, called multiple tumor suppressor, encodes a special protein for the inhibition of cell division and has recently been found to be deleted on a frequent basis in cell lines from tumors of the breast, lung, brain, skin, kidney, bladder and other sites. This finding will open up new targets for novel therapy development and is yet another reminder of the powerful impact of a basic research agenda in ways that are not always predictable.

As there is increasing ability to detect very small tumors and to identify rapidly growing tumors, there may be increasing potential to treat more effectively and to reduce cancer mortality.

Today, nearly 70 gene therapy protocols using a number of approaches have been approved. Gene therapy techniques are being used experimentally to treat melanoma, kidney cancer, small and nonsmall cell lung cancer, ovarian and breast cancers, neuroblastomas, glioblastomas and other cancers as well.

We know a great deal about oncogenes, genes that drive tumor growth, and suppressor genes, genes whose normal function is to put the brakes on tumor growth.

For example, p53, which is a mutated tumor suppressor protein, or ras, which may be a mutated oncogene protein, are being used in a customized vaccine program in our intramural program trying to stimulate the body's own immunity against a patient's own tumor.

ENVIRONMENTAL STUDIES

The environmental and occupational aspects of cancer are of surpassing importance. Thus, NCI scientists are examining the effects of environmental and occupational exposures as well as the interaction between heredity and the environment, including examination of issues of high public concern such as pesticides, air pollution, radon, electromagnetic fields, cellular telephones and a host of other factors.

BREAST CANCER

Breast cancer rates in the Northeast and the mid–Atlantic States are high, and several epidemiological studies are under way or being planned to explore the reasons for these high rates.

For example, we have a highly focused study on Long Island, which is looking at the various factors contributing to breast cancer, including electromagnetic exposures, water, airplane exhaust, organic solvents, polychlorinated biphenyls and a number of other possible environmental carcinogens.

AGRICULTURAL STUDIES

Because modern agricultural practice has relied heavily on chemicals, NCI scientists are looking to see if this is related to a high incidence of certain types of cancers in farmers. A major agricultural study is being carried out by the National Cancer Institute in collaboration with the Environmental Protection Agency and our sister Institute, the National Institute of Environmental Health Sciences. The study is based in Iowa and North Carolina. About 100,000 farm workers and their families are being studied to determine the etiologic contribution of pesticides, chemicals, viruses and other exposures.

Lung cancer and other tobacco-related cancers continue to end lives and devastate American families. We have a number of programs that are addressing this issue.

PREVENTION

As part of a broad cancer prevention research program, the National Cancer Institute collaborates with private and trade organizations on the Five-A-Day for better health campaign, a campaign to encourage the intake of more fruits and vegetables.

Other programs focus on specific audiences and address certain life-styles. These include the National Black Leadership Initiative on Cancer, the National Hispanic Leadership on Cancer, and the Appalachian Leadership on Cancer. We are highly focused on the relationship between cancer and poverty.

The Prostate Cancer Prevention Trial and the Breast Cancer Prevention Trial using finasteride and tamoxifen, respectively, as experimental agents are both under way. Both trials will include a genetic analysis of biopsies to explore both inherited and acquired genetic mutations to see if special populations can be identified both as to benefit and risk.

Chemoprevention and bionutrition are becoming important cancer prevention strategies. Vitamin A agents such as retinoids and beta carotene have been shown to be effective in preventing certain types of head and neck tumors and have other benefits as well in the cardiovascular arena, at least on an epidemiologic basis. But recent clinical trials suggest that for very heavy smokers, lung cancer rates may not be affected by beta carotene and may actually be worsened, thus providing a warning to relying on over simplified assumptions.

DIAGNOSIS

Until simple tests are available to screen for the molecular signs of cancer, NCI is stimulating research on a number of diagnostic tools. For example, while conventional mammography definitely reduces mortality in women over the age of 50, there is a strong need for new and better methods to detect early tumors in younger women. Digital mammography methods may offer more accurate detection of breast cancer. Magnetic resonance imaging is being used to explore new ways of detecting the disease.

A large screening clinical trial, the Prostate, Lung, Colorectal and Ovarian cancer trial (PLCO), is assessing the predictive value of such tests as PSA, ultrasound and CA125. About 30,000 men and 30,000 women will be enrolled with equal numbers as controls.

DRUG DEVELOPMENT

NCI scientists have contributed to the development of a majority of cancer drugs now approved by the FDA. Taxol, pentostatin, fludarabine, deoxycoformycin and a number of other drugs have been approved in recent years. Taxol is approved for ovarian cancer and now has been approved for breast cancer.

AIDS

NCI has made many contributions to AIDS research, including a recent finding that cell-mediated immunity is present in some individuals who remain healthy despite exposure to HIV. This observation has implications for treatment as well as the development of an AIDS vaccine.

From the onset of the AIDS pandemic, the NCI–AIDS drug screen and drug development program has been a national resource and has led to the development of several agents now approved by the Food and Drug Administration and in widespread use. To find promising agents, the NCI has tested nearly 140,000 agents for anti–AIDS activity, including a number of natural products.

QUALITY CONTROL

In conclusion, although there are important achievements in cancer research, there should be no illusions as to the challenge ahead. Our challenges are not confined to science alone. We recently had to ask for the removal of a principal investigator and to institute a number of other changes on a major clinical trial cooperative agreement for untimeliness in auditing and publishing practices, including a tardiness in publishing a reanalysis of a major clinical trial in which one surgeon in a hospital in Montreal falsified data.

This is a reminder that quality control and audit functions cannot be taken for granted, and the President's budget gives us the flexibility to address these issues.

Cancer and AIDS present the most formidable challenge in science and medicine today, in my opinion. They require our total commitment, and the NCI has an indispensable role to play.

Mr. Chairman and Members of the Committee, the FY 1995 budget request is $1,967,709,000. I appreciate the opportunity to testify before this Committee and would be very pleased to answer any questions.

Mr. SMITH. Thank you.

[The prepared statement and biography of Dr. Samuel Broder follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Cancer Institute

This is a time of significant progress in cancer research, but it is also a time of considerable challenge. A number of cancers are on the rise, notably breast, prostate, and lung cancers. NCI foundation stones of basic cancer research, clinical trials, and a nationwide network of cancer centers provide the optimal basis for the new discoveries needed to improve cancer prevention and cancer care in the community. Translation of advances into clinical practice is speeded by the NCI Specialized Programs of Research Excellence (SPOREs) in breast, prostate, lung and, most recently, gastrointestinal cancers. Diffusion of research results to the public and the professional and research communities is carried out through the Cancer Information Service, PDQ, CANCERFAX, Cancer Net and the Journal of the National Cancer Institute.

A number of genes involved in specific cancers have been isolated. For instance, a gene named MSH2, involved in as many as 1 in 6 colon cancers, was identified this year. This gene also appears to be involved in a number of other cancers as well. Each new genetic discovery guides the development of specific diagnostic approaches, interventions, and treatments. For instance, an experimental blood test has been developed for another genetic mutation that predisposes individuals to a rare, inherited type of colon cancer, known as familial adematous polyposis (FAP). As there is increasing ability to detect very small tumors and to identify rapidly growing tumors, there will be increasing ability to treat appropriately and to reduce cancer mortality.

Today, nearly 70 gene therapy protocols, using varied approaches, have been approved. Gene therapy techniques are being used experimentally to treat melanoma, kidney cancer, small cell and non-small cell lung cancer, ovarian and breast cancers, neuroblastomas, glioblastomas, and various lymphomas and leukemias as well as immune disorders and cystic fibrosis.

This field of gene therapy provides an example of how cancer research progresses from over 20 years of research in genetics, immunology and biotechnology to safety and efficacy studies and then into clinical application. This field was so new that a new advisory structure had to be created. Finally, in August 1990, two little girls with a serious, genetically determined immune disorder were treated with gene therapy. They have continued to do well and are now attending school. This pilot study was the result of teamwork involving NCI and the National Heart, Lung and Blood Institute.

Throughout medical history, vaccines against bacteria and viruses have protected against deadly infectious diseases. There are similar hopes for cancer vaccines. A new vaccine combines the gene for carcinoembryonic antigen (CEA) with vaccinia virus. To date, 20 patients with gastrointestinal, breast or lung cancer have been inoculated with CEA-vaccinia vaccine. In another approach, p53, a mutated tumor suppressor protein, is used as a vaccine to stimulate killer T cells which attack the tumor.

NCI scientists are examining the effects of environmental and occupational exposures as well as the interaction between heredity and environment, including examination of issues of high public concern such as radon, electromagnetic fields, and cellular telephones.

Breast cancer rates in the Northeast and in the mid-Atlantic states are high, and several epidemiological studies are being planned to explore the reasons for these high rates. For example, the Long Island Breast Cancer Study Project is looking at the various factors contributing to breast cancer, including factors such as electromagnetic exposures, water, airplane exhaust, organic solvents, polychlorinated biphenyls (PCB) and polybrominated biphenyls (PBB), and pesticides which will be examined in conjunction with case-controlled studies of women in the community.

Because modern agricultural practice has relied heavily on chemicals, scientists are looking to see if this is related to high incidence rates of cancer in farmers. A major epidemiologic study is being carried out by NCI, the Environmental Protection Agency, and the National Institute of Environmental Health Sciences. About 100,000 farm workers and their families are being studied to determine the etiologic contributions of pesticides, chemicals, viruses, and other exposures.

Lung cancer and other tobacco-related cancers continue to end lives and devastate American families. NCI addresses these cancers through basic research on carcinogenesis as well as smoking control programs such as the American Stop Smoking Intervention Study (ASSIST) conducted with the American Cancer Society and state health departments. ASSIST will reach more than 91 million people in 17 states.

As part of a broad cancer prevention research program, NCI collaborates with the 5-A-Day for Better Health campaign to encourage the intake of more fruits and vegetables. Other programs focus on a specific audience and address many lifestyle factors. These include the National Black Leadership Initiative on Cancer, the National Hispanic Leadership Initiative on Cancer, and the Appalachian Leadership Initiative on Cancer.

The Prostate Cancer Prevention Trial and the Breast Cancer Prevention Trial, using finasteride and tamoxifen respectively as experimental agents, are both well under way. Both trials will include genetic analysis of biopsies to explore both inherited and acquired genetic mutations. Chemoprevention and bionutrition are becoming important cancer prevention strategies. Vitamin A-related agents, such as the retinoids and beta-carotene, have been shown to be effective in preventing second head and neck tumors.

Until simple tests are available to screen for molecular signs of cancer, NCI is stimulating research on new diagnostic tools. While conventional mammography definitively reduces mortality in women over age 50, the same benefit has not been demonstrated for younger women as a group. Thus, there is a serious need for new and better methods to detect early tumors in young women. Digital mammography methods may offer more accurate detection of breast cancer with better images, less radiation and the potential for electronic image transfer. Magnetic resonance imaging is being used to explore new ways of screening women for breast cancer.

A large screening clinical trial, the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Trial, is assessing the predictive value of such tests as PSA, ultrasound, and CA125. About 37,000 men and 37,000 women will be enrolled with equal number as controls.

NCI scientists have contributed to the development of the majority of cancer drugs now approved by the FDA. Taxol®, pentostatin, fludarabine, and deoxycoformycin have been approved within the last two years. Taxol is approved for ovarian cancer and is expected to be approved for breast cancer. Currently, Taxol is being tested in various combination therapies. Research continues on analogues such as Taxotere and semi-synthetic and synthetic versions. More than 200 agents are in preclinical development.

NCI has made many contributions to AIDS research, including a recent finding that cell-mediated immunity is present in some individuals who have remained healthy despite exposure to HIV. This observation has implications for treatment as well as the development of an AIDS vaccine. Women are increasingly being infected with the virus and perinatal transmission to the infant is a very serious problem. One NCI study of twins suggests exposure in the birth canal is involved in transmission of the virus which points to possible use of an inexpensive viricidal solution to cleanse the birth canal to lower the risk of infection during delivery. From the onset of the AIDS pandemic, the NCI AIDS drug screen has been a national resource. To find promising agents against AIDS, NCI has tested more than 137,000 agents for anti-AIDS activity, including a number of natural products.

In conclusion, although there are important achievements in cancer research, there should be no illusions as to the challenge ahead. Cancer and AIDS present the most formidable challenges in science and medicine today. Mr. Chairman, the FY 1995 Budget request for NCI is $1,967,709,000. I appreciate the opportunity to testify before this Committee and will be pleased to answer any questions you might have.

CURRICULUM VITAE
SAMUEL BRODER, M.D.

PERSONAL: b. February 24, 1945; US citizenship
Married, two children

EDUCATION:
University of Michigan, Ann Arbor, MI

1966	B.S. - College of Literature, Science and the Arts (high honors)
1970	M.D. - School of Medicine (cum laude)

EMPLOYMENT:
Stanford University, Palo Alto, CA

1970-1971	Internship (Medicine)
1971-1972	Residency (Medicine)

National Cancer Institute, National Institutes of Health, Bethesda, MD

1972-1975	Clinical Associate, Metabolism Branch
1975-1976	Investigator, Medicine Branch
1976-1981	Senior Investigator, Metabolism Branch
1981-1988	Associate Director, Clinical Oncology Program
1989-pres	Director, National Cancer Institute

BOARD CERTIFICATIONS and LICENSES:

1973	Certified in Internal Medicine
1977	Certified in Medical Oncology
	Licensed to practice Medicine in California and Maryland

SOCIETIES and ORGANIZATIONS:
American Society for Clinical Investigation (elected 1980)
Association of American Physicians (elected 1989)
American Federation for Clinical Research (Eastern Section Councilor)
American Association for Cancer Research
American Society for Clinical Oncology
American Association of Immunologists
Clinical Immunology Society
Editor, Symposium on HTLV, September 1985, Cancer Research
Editor, AIDS: Modern Concepts and Therapeutic Challenges
Editor, Molecular Foundations of Oncology
Editorial Advisory Board for numerous journals
Fellow, American College of Physicians

HONORS:
Phi Beta Kappa
Alpha Omega Alpha
Fellow of the Life Insurance Medical Research FundUpjohn Achievement Award
Arthur S. Flemming Award
Public Health Service/Meritorious Service Medal
Public Health Service/Distinguished Service Medal
Thirty-seventh Augustus B. Wadsworth Lectureship

HONORS:

- Third Mullin Lectureship/University of Scranton
- Fourth Biennial Chemistry as a Life Science
- Lectureship/Rutgers University
- Twelfth Annual CIBA-GEIGY DREW Award in Biomedical Research
- Alpha Omega Alpha Distinguished Professor/Dartmouth Medical School
- Robert T. Wong, M.D. Endowment Award/University of Hawaii Foundation
- Samuel Rudin Award/Columbia Presbyterian Hospital
- First Annual Award for Outstanding Achievement in International Health/Institute for International Health and Development
- Gilman Honors Award/New York University
- Harvey W. Wiley Medal/FDA Commissioner's Special Citation
- 10th Annual Calabresi Lecture/Brown University
- Health Leader of the Year Award/Commissioned Officers Association, 1990
- Dr. Frederick Stohlman Lecture Award/Volga Wilsede Meeting
- Lifetime Science Award/Institute for Advanced Studies in Immunology & Aging
- Honoree, World AIDS Day 1990/American Foundation for AIDS Research
- National Hispanic Health Leadership Award
- Honoree, American Cancer Society
- John K. Lattimer Award/American Urological Association
- Public Service Leadership Award/National Coalition for Cancer Survivorship
- Presidential Certificate of Appreciation/National Medical Association
- Surgeon General's Exemplary Service Medal
- First Herbert J. Block Memorial Lectureship Award/Ohio State University
- Comprehensive Cancer Center and Arthur G. James Cancer Hospital & Res. Institute
- Griffuel Prize, 1992

MAJOR PROFESSIONAL INTERESTS:

Relationship between cancer and immunodeficiency states; anti-retroviral chemotherapy

OPENING STATEMENT

Dr. OLDEN. Thank you, Mr. Chairman, and Committee Members. It is a pleasure to appear before this distinguished panel.

From conception to death, humans are exposed to a multitude of environmental agents, including foods and nutrients, physical agents such as heat, ionizing and nonionizing radiation, social and economic factors that affect health and behavior, lifestyle choices and substance abuse and synthetic and naturally occurring chemicals.

The mission of the National Institute of Environmental Health Sciences is to determine how these environmental exposures affect our health, how individuals differ in susceptibility to these exposures and how these susceptibilities change with age. To fulfill the mission, the Institute must provide the science necessary to understand the impact of the environment on human health, must translate this information into prevention intervention strategies and must communicate this information to the American people.

Opportunities now exist for NIEHS to capitalize on improved techniques in molecular biology and computational chemistry to unravel the mechanisms by which environmental agents perturb normal biological processes. That more mechanistic approach will be used to improve human risk assessment and to develop prevention and intervention strategies. Risk assessment decisions form the basis of Federal, State and local laws and regulations that require the expenditures of billions of dollars to reduce potentially harmful human exposures.

NIEHS has targeted five areas of emphasis as critical to the risk assessment process. They are basic biology of environmental disorders, hazard identification and characterization, molecular prevention, intervention, development of alternative methods and models to improve extrapolation from rodents or animals to humans, and environmental justice. And I will discuss those five in sequence.

First, basic biology of environmental disorders. To date, a large part of environmental health science research has focused on identifying the environmental causes of diseases. Future research promise lies in understanding the actual molecular and genetic basis of environmentally caused diseases. Good health depends on the proper functioning of genes, which control cellular growth, differentiation and death.

When critical genetic material is altered, the function over which the genes exert control can go awry, leading to birth defects, cancer, neuro-behavioral abnormalities and other diseases and dysfunctions. Human health also depends on a complex network of chemical signals between cells. The molecules that transmit these signals are primary targets of toxic substances in the environment.

Identification of the role of individual protein messengers and receptors in cellular determination, growth, differentiation and responsiveness, and understanding the ability of environmental chemicals to interact with these critical proteins is of importance to NIEHS research priorities. Research in this area holds promise for defining the roles that environmental agents play in a host of diseases and dysfunctions, including infertility, birth defects, neurological disorders, immune dysfunctions and other chronic diseases.

The variation in individual response to environmental agents is exceptionally wide. This variation is accounted for by differences in metabolism, DNA repair capacity or genetic predisposition to specific diseases. It is because of this large diversity in responsiveness to environmental toxicants that risks to environmental agents have been difficult to pinpoint, particularly at low exposures.

Opportunities now exist for studies of genetic susceptibility for cancer and other diseases in which an environmental component can be presumed. Environmental factors contribute to many of the disease processes that are specific to or predominate in women. For example, heavy metals have been shown to accelerate osteoporosis, a bone disorder affecting most women over age 60.

A number of widespread environmental toxins such as DDT and the PCBs mimic the female hormone estrogen and can play a role in hormonally related cancers such as those of the breast, the uterus and the ovaries. Environmental estrogens could also be important components of benign proliferative disorders of the female reproductive tract such as endometriosis and uterine fibroids.

Many environmental compounds affect reproduction, leading to infertility, premature birth or birth defects.

Similarly, children's health is also a priority of the National Institute of Environmental Health Sciences. The developing fetus and infant represents particularly vulnerable targets for environmental agents, and adverse effects sustained at this time can cause health problems throughout the individual's life. These problems may even be apparent many years after the original exposures.

Finally, greater emphasis has been assigned to human studies with the development of a clinical program.

The NIEHS has started several new clinical research activities. One is a multi-center project, which will examine the efficacy of the oral chelator succimere, to treat children with low blood lead levels. Another program will make use of local medical centers in the Raleigh–Durham area to mail their clinical research with the laboratory research ongoing at NIEHS.

Initial studies will look at environmental factors that promote asthma, dysfunctions of reproductive endocrinology, and the degenerative neurological diseases, hazard identification and characterization.

Use of traditional animal tests and epidemiologic studies to identify environmental hazards to human health will remain a cornerstone of the Nation's prevention intervention program at NIEHS. The strategy of these techniques will be greatly improved with incorporation of new insights concerning the molecular basis of toxic effects into animal testing and human epidemiologic studies.

However, animal studies often provide only descriptive information, revealing the toxicity of an environmental agent by its ability to cause effects such as tumors, histopathologic abnormalities or genetic chance.

An even more meaningful way to relate animal studies to human health effects is by determining the underlying mechanism leading to toxicity. Hazard identification is often handicapped by our inability to determine individual exposure levels or to account for individual differences in uptake and distribution of toxicants.

As our knowledge of the molecular components of environmental exposures increase, biological indicators measuring both exposure and effect can be developed for use in both epidemiologic and testing studies. Potentially, biomarkers could be used for screening programs in exposed human populations to provide early warning of environmental exposure, predict development of disease and enable clinicians to describe appropriate preventive strategies.

Prevention intervention. Further understanding of the environmental components and basic biology of disorders can lead to prevention and intervention strategies to circumvent many adverse health effects. Traditionally, these strategies have focused on primary prevention techniques such as eliminating or reducing environmental exposures. These techniques will continue to be important as part of the Nation's environmental health program.

An integral part of this program is the development of the science that will enable risk assessors to determine how much reduction of exposure is needed to protect public health. Generating risk assessment levels relies strongly on rodent data and on extrapolation of results in rodents to probable effects in humans. The relevance and power of these assessment schemes will be greatly enhanced when the biological mechanism for adverse effects are incorporated into mathematical models used to estimate risks from low exposures.

As we understand the molecular basis of environmentally induced disease, secondary intervention prevention technique could be developed to treat people following adverse environmental exposures. These molecular intervention techniques would rely on manipulation of the biological mechanisms underlying environmentally induced diseases such as activating inactivated enzymes, receptors and other molecular components. They would be particularly useful in dealing with environmental exposures that are ubiquitous or difficult to eliminate.

They also would have important implications for the pharmaceutical and pesticide industries, which could in the future develop products with maximal effectiveness and minimal side effects, based on structural understanding of underlying biological mechanisms.

Development of alternative methods. Assessment of potential adverse health effects of chemicals have been accomplished largely by testing these substances in laboratory animals. While such tests have been useful in identifying human health hazards, improved test methods are needed that are more predictive, that can be achieved in a shorter time frame and that are more cost-effective.

There is also an expectation from the public that the scientific community will increase efforts to develop new alternative methods that will reduce animal use, replace animals with nonanimal methods or lower species, where possible, and refine animal use to eliminate or further minimize pain and distress.

Research and development efforts will emphasize—first, we will develop genetically engineered cell lines to characterize the biological activity and toxicity of profiles of chemical at the molecular level.

We will develop transgenic animals that more closely model human response to toxic substances.

We will systematically investigate nonmammalian and invertebrate species to identify functional and structural attributes that may be useful as research or testing models.

Fourth is further characterize the similarities and differences between animal testing models and humans to enhance the usefulness of this information in the risk assessment process.

And, finally, to improve computer-based prediction modeling systems for specific toxicologic endpoints.

And, finally, environmental justice. Environmental justice is a newly emerging social issue. It refers to the fact that where one lives is a matter largely dependent upon socioeconomic factors. Intuitively, one would expect that the poor and politically disenfranchised are at greater risk of living near polluting industries, hazardous waste sites or working in hazardous occupations. For these reasons, they would be more likely to suffer from environmentally related diseases than those in the middle and upper classes.

It is a logical extension of the Institute's mission to explore the dimension of the Nation's environmental justice problem. To this end, NIEHS is presently supporting three environmental justice research centers at major institutions and a large multi-institutional clinical trial to improve the treatment of lead poisoning.

A national conference focusing on environmental justice was held in February, 1994, that attracted more than 1,100 participants here in the D.C. area.

Finally, NIH is supporting three environmental health science centers that focus on research on agricultural chemicals, and, in fact, more than 90 percent of agricultural workers are Hispanic or ethnic minorities.

The budget request this year by the President for our Institute is $267,955,000. This request, inconjunction with the funds provided through the Super Fund Basic Research Program, will be adequate to advance the research agenda outlined above in times of economic constraints, and difficult choices have to be made. However, I am pleased that environmental research has been assigned a high priority in this administration.

I thank you, Mr. Chairman, and I would be pleased to respond to any questions that you might have.

[The prepared statement and biography of Dr. Kenneth Olden follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Environmental Health Sciences

From conception to death, humans are exposed to a multitude of environmental agents, including foods and nutrients, physical agents such as heat and ionizing and non-ionizing radiation, social and economic factors that affect our health and behavior, lifestyle choices and substance abuse, and synthetic and naturally occurring chemicals. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to determine how these environmental exposures affect our health, how individuals differ in their susceptibility to these effects, and how these susceptibilities change with age. To fulfill this mission, the Institute must provide the science necessary to understand the impact of the environment on human health, must translate this information into prevention and intervention strategies and must communicate this information to the American people.

Opportunities now exist for the NIEHS to capitalize on improved techniques in molecular biology and computational chemistry to unravel the mechanisms by which environmental agents perturb normal biological processes. This more mechanistic approach will be used to improve human risk assessment and to develop prevention or intervention strategies. Risk assessment decisions form the basis of Federal, State and local laws and regulations which require the expenditure of billions of dollars to reduce potentially harmful human exposures. NIEHS has targeted five areas of emphasis as critical to the risk assessment process: basic biology of environmental disorders; hazard identification and characterization; molecular prevention and intervention; development of alternative methods; and environmental justice.

Basic Biology of Environmental Disorders: To date a large part of environmental health research has focused on identifying the environmental causes of diseases. Future research promise lies in understanding the actual molecular and genetic basis of environmentally caused disorders.

Good health depends on the proper functioning of genes which control cellular growth, differentiation and death. When critical genetic material is altered, the functions over which it exerts control can go awry, leading to birth defects, cancer, neurobehavioral abnormalities, and other diseases and dysfunctions.

Human health also depends on a complex network of chemical signals between cells. The molecules that transmit these signals are primary targets of toxic substances in the environment. Identification of the role of individual protein messengers and receptors in cellular determination, growth, differentiation, and responsiveness, and understanding the ability of environmental chemicals to interact with these critical proteins is an important NIEHS research priority. Research in this area holds promise for defining the roles that environmental agents may play in a host of diseases and dysfunctions, including infertility, birth defects, neurological disorders, immune dysfunctions, and chronic diseases.

The variation in individual response to environmental agents is exceptionally wide. This variation is accounted for by differences in metabolism, DNA repair capacity, or genetic predisposition to specific diseases. It is because of this large diversity in responsiveness to environmental toxicants that risks to environmental agents have been difficult to pinpoint, particularly at low exposures. Opportunities now exist for studies of genetic susceptibility for cancer and other diseases in which an environmental component can be presumed.

Of particular interest to the NIEHS are environmental components of women's, children's, and minority health. Environmental factors contribute to many of the disease processes that are specific to, or predominate in, women. For example, heavy metals have been shown to accelerate osteoporosis, a bone disorder affecting most women over age 60. A number of widespread environmental toxicants such as DDT and PCBs mimic the female hormone estrogen and could play a role in hormonally related cancers such as those of the breast, uterus, and ovaries. Environmental estrogens could also be important components of benign proliferative disorders of the female reproductive tract, such as endometriosis and uterine fibroids. Many environmental compounds affect reproduction, leading to infertility, spontaneous abortion, or birth defects.

Similarly, children's health is also a priority of the NIEHS. The developing fetus and infant represent particularly vulnerable targets for environmental agents. An adverse effect sustained at this time can cause health problems throughout an individual's life. These problems may not even be apparent until many years after the original exposure.

Finally, greater emphasis has been assigned to human studies with the development of a clinical program. The NIEHS has started several new clinical research programs. One multi-center project will examine the efficacy of an oral chelator, succimer, to treat children with low blood lead levels. Another program will use local medical centers to meld their clinical research with the laboratory research ongoing at NIEHS. Initial studies will look at environmental factors that promote asthma, dysfunctions of reproductive endocrinology, and degenerative neurological diseases.

Hazard Identification and Characterization: Use of traditional animal testing and epidemiologic studies to identify environmental hazards to human health will remain a cornerstone of the Nation's prevention and intervention program. The strength of these techniques will be greatly improved with incorporation of new insights concerning the molecular basis of toxic effects into animal testing and human epidemiology studies. However, animal studies often provide only descriptive information, revealing the toxicity of an environmental agent by its ability to cause adverse effects such as tumors, histopathologic abnormalities, or genetic changes. An even more meaningful way to relate animal studies to human health effects is by determining the underlying mechanisms leading to toxicity.

Hazard identification is often handicapped by an inability to determine individual exposure levels or to account for individual differences in uptake and distribution of toxicants. As our knowledge of the molecular components of environmental exposures increases, biological indicators measuring both exposures and effects can be developed for use in both epidemiologic and testing studies. Potentially, biomarkers could be used in screening programs for exposed human populations to provide early warning of environmental exposure, predict development of disease, and enable clinicians to prescribe appropriate intervention therapies.

Prevention and Intervention: Further understanding of the environmental components and basic biology of disorders can lead to prevention and intervention strategies to circumvent many adverse health effects. Traditionally these strategies have focused on primary prevention techniques such as eliminating or reducing environmental exposures. These techniques will continue to be important parts of the Nation's environmental health programs. An integral part of this program is the development of the science that will enable risk assessors to determine how much reduction of exposure is needed to protect public health. Generating risk assessment levels relies strongly on rodent data and on extrapolation of results in rodents to probable effects in humans. The relevance and power of these assessment schemes will be greatly enhanced when the biological mechanisms for adverse effects are incorporated into the mathematical models used to estimate risks from low exposures.

As we understand the molecular and cellular basis of environmentally induced diseases, secondary prevention and intervention techniques could be developed to treat people following an adverse environmental exposure. These molecular intervention techniques would rely on manipulations of the biological mechanism underlying environmentally induced diseases, such as activating and inactivating enzymes, receptors, and other molecular components. They would be particularly useful in dealing with environmental exposures that are ubiquitous or difficult to eliminate. They also would have important implications in the pharmaceutical and pesticide industries, which could in the future develop products with maximal effectiveness and minimal side effects based on a structural understanding of underlying biological mechanisms.

Development of Alternative Methods: Assessment of the potential adverse health effects of chemicals has been accomplished largely by testing these substances in laboratory animals. While such tests have been useful in identifying human health hazards, improved test methods are needed that are more predictive, that can be achieved in a shorter timeframe, and that are more cost-effective. There is also an expectation from the public that the scientific community will increase efforts to develop new "alternative" methods that will reduce animal use, replace animals with non-animal methods or lower species where possible, and refine animal use to eliminate or further minimize pain and distress.

Research and development efforts will: (1) develop genetically engineered cell lines to characterize the biological activity and toxicity profiles of chemicals at the molecular and cellular level; (2) develop transgenic animals that more closely model the human response to toxic substances; (3) systematically investigate non-mammalian and invertebrate species to identify functional and structural attributes that may be useful as research or testing models; (4) further characterize the similarities and differences between animal testing models and humans to enhance the usefulness of this information in the risk assessment process; and (5) improve computer-based prediction and modelling systems for specific toxicologic endpoints.

Environmental Justice: Environmental justice is a newly emerging social issue. It refers to the fact that where one works and lives is a matter of choice largely dependent upon socioeconomic factors. Intuitively, one would expect that the poor and politically disenfranchised are at a greater risk of living near hazardous waste sites or working at hazardous occupations. For these reasons they would be more likely to suffer from environmentally related diseases than would those in the middle and upper socioeconomic classes. It is a logical extension of the Institute's mission to explore the dimensions of the Nation's environmental equity problem.

To this end, the NIEHS is presently supporting three environmental justice research centers and a large multi-institutional clinical trial to improve the treatment of lead poisoning. A national conference focusing on environmental justice held in February 1994 attracted more than 1100 participants.

The main objective of this program is to establish a new research paradigm linking members of the community who are directly affected by adverse environmental conditions with researchers and health care providers. Development of community-based strategies to address environmental health problems requires approaches that are not typically familiar to the research and medical communities. The distinctive needs of individual communities and their inhabitants are often neglected in identifying environmental health problems and devising appropriate medical intervention tactics.

This budget request of $267,955,000 is adequate to advance the research agenda outlined above. In times of economic constraints difficult choices have to be made; however, I am pleased that environmental research has been identified as a priority for the Nation.

Mr. Chairman, thank you for the opportunity to appear before your Committee. I will be pleased to answer any questions that you may have.

OLDEN, DR. KENNETH

Director, National Institute of Environmental Health Sciences (NIEHS) and Director, National Toxicology Program (NTP)

July 22, 1938. Parrottsville, Tennessee

Education: B.S., Knoxville College, 1960; M.S., University of Michigan, 1964; Ph.D., Temple University, 1970 (research done in absentia at the University of Rochester).

Professional History: 1964-65, Research Assistant, Department of Biological Chemistry, Columbia University. 1970-74, Research Fellow and Instructor of Physiology, Harvard University Medical School. 1974-77, Senior Staff Fellow, Division of Cancer Biology and Diagnosis, National Cancer Institute. 1977-78, Expert (Biochemistry) Division of Cancer Biology and Diagnosis, National Cancer Institute. 1978-79, Research Biologist, Division of Cancer Biology and Diagnosis, National Cancer Institute. 1979-82, Associate Director for Research, Howard University Cancer Center, and Associate Professor of Oncology, Howard University Medical School. 1982-84, Associate Director for Research and Deputy Director, Howard University Cancer Center, and Associate Professor of Oncology, Howard University Medical School. 1984-85, Associate Director for Basic Research and Deputy Director, Howard University Cancer Center, and Professor of Oncology, Howard University Medical School. 1985-91, Director of the Howard University Cancer Center and Professor and Chairman of the Department of Oncology, Howard University Medical School. 1991-present, Director, NIEHS and NTP.

Professional Organizations: American Society for Cell Biology; American Society of Biological Chemistry; American Association of Cancer Research; Society for Biological Response Modifiers; Metastasis Research Society.

Honors, Awards: Porter Development Postdoctoral Fellow, 1970. NIH Postdoctoral Fellow, 1970-73. Macy Faculty Fellow, 1973-74. Citation Classic, Current Contents, Life Sciences, 1980. Member, Division of Cancer Biology and Diagnosis Board of Scientific Counselors, National Cancer Institute, 1981-85. Member, Public Policy Committee of the American Society for Cell Biology, 1984. Co-Chairman, Mid-Atlantic Region of National Black Leadership Initiative on Cancer, 1987-89. Member, Board of Directors, Association of American Cancer Institutes, 1987-90. Member, Division of Cancer Treatment Board of Scientific Counselors, National Cancer Institute, NIH, since 1988. Selected as "One of sixteen historical and contemporary role models" for the Museum of Science and Industry exhibit on Black Achievers in Science, Museum of Science and Industry, Chicago, IL, 1988. Member, Board of Directors of Association of Minority Health Professions Schools, 1988-present. Member and Co-Chairman of National Advisory Committee on Socio-Economically Disadvantaged of The American Cancer Society, 1988. Member, Advisory Panel Council for Cell Biology, National Science Foundation, 1989-90. Presidential appointment to membership on the

National Cancer Advisory Board, 1991. Associate Editor of _Cancer Research_, _The Journal of the National Cancer Institute_, _Cell Regulation_, and _Environmental Health Perspectives_.

Mr. SERRANO [presiding]. I think what we want to do, in view of the fact that there is a vote on and there are Members who are voting and have to vote, is to take a short recess until the Chairman arrives again. Then we will continue. Thank you.

[Recess.]

OPENING STATEMENT

Dr. LÖE. Thank you, Mr. Chairman.

As you have heard, I am leaving NIH this summer, so this is the twelfth and the last time that——

Mr. SMITH. [presiding]. How many times?

Dr. LÖE. Twelfth.

This is the last time I will appear before this Committee, and I want to take this opportunity to thank you and each Member of this subcommittee for your interest, your encouragement, and your advice during these years.

Mr. SMITH. Well, we want to thank you for the years you spent at this.

Dr. LÖE. It has been a privilege and a pleasure to come before you every year and to share both the problems and the pride that we take in our accomplishments. I speak on behalf of the entire NIDR when I say that we are most grateful for your support.

The mission of the NIDR, as stated at the time of its establishment in 1948, and as it has been for the past 46 years of this Institute's existence, is to improve the oral health of the American people. We decided in the early 1980s that it was important to assess how well we were doing and that, therefore, a broad-based program in oral epidemiology should be established.

The national surveys that we conducted during 1985 to 1987 showed that 50 percent of the 40 million schoolchildren of America had never had a cavity in their permanent teeth and that substantial improvement had occurred in the adult population as well. From these and other data it was estimated that the total annual dental expenditures, adjusted for inflation, grew very slowly during the decade of the 1980s, even in light of the fact that more and more Americans were seeking dental care.

It was also documented that the ability of dentistry to hold the line on health care costs was directly related to advances in oral health research. Economists estimated that the declines in toothlessness and in the prevalence and severity of oral disease translated into savings of approximately $5 billion in the Nation's dental bill in 1989. This is a savings in one year of over two times the total appropriation for the NIDR from its inception in 1948 through the current year 1994.

I do not want to mislead you, Mr. Chairman, into thinking that the Nation's oral health problems have disappeared. Every one of us remains at risk for oral disease, and for millions of Americans these are severe problems. While it is heartening to note that half of the children have no cavities, this also means that 50 percent still do.

We also know that blacks and Hispanics have worse oral health than whites. Our oldest citizens have the worst oral health of all, with over 40 percent having lost all their teeth, and those who still have teeth continue to get cavities and suffer the most severe and extensive periodontal diseases of any age group.

Besides providing an inventory and serving as a basis for cost estimates and assessments of demand for dental professionals and auxiliary personnel, the data analysis also fostered a planning effort and an evolution of the oral health sciences from a narrow concern with teeth and gums to encompass all the oral and craniofacial tissues in health and disease. This evolution was outlined in two long-range research plans entitled "Challenges for the Eighties" in 1983, and "Broadening the Scope" in 1990.

Because the mouth mirrors the overall health of an individual, our mission includes research on systemic diseases that affect the oral and craniofacial tissues, as well as on the effects of oral disease on the rest of the body. Thus, our investigators study diseases like AIDS and diabetes, both of which have conspicuous oral signs and complications. We also study diseases more common in women, such as osteoporosis, and Sjögren's syndrome, a condition in which the salivary and tear glands are destroyed.

In general, our goals for the nineties include research aimed at improving the oral health of all individuals at high risk because of medically compromising or handicapping conditions or because of limited ability or access to care, groups that include the elderly and members of racial and ethnic minorities.

In supporting this broad research agenda, the NIDR has emphasized investigator-initiated research project grants and promoted the use of comprehensive research centers. In short, during this past decade, the emphasis was on connecting the mouth with the rest of the body.

In order to do that, it was necessary to increase the research capacity of the dental schools throughout the country by expanding the research centers program in basic and categorical research, and developing a novel training program for careers in science through the Dentist-Scientist Program. Today, there are more research-intensive dental schools than in the early 1980s, and the number of ably trained researchers has increased.

Finally, strengthening the partnership with the practicing profession and the public became a special goal for the Institute, placing emphasis on science transfer and communication. The Institute implemented a variety of means to convey research findings from the laboratory to the profession and to the public.

NIDR launched a series of continuing dental education conferences for practitioners entitled "Scientific Frontiers in Clinical Dentistry," attracting hundreds of practitioners from throughout the country. Recently we established the National Oral Health Information Clearinghouse as a resource center for educational materials aimed at "special needs" patients whose medical conditions compromise oral health. Working with voluntary organizations like the National Alliance for Oral Health and the American Fund for Dental Health, we are now engaged in a national oral health promotion campaign.

It is, of course, difficult to give justice to the many activities that filled these almost 12 years of my tenure at the NIDR, but I leave with the satisfaction of knowing that there are people and programs in place and that both are well poised to meet the challenges of the future.

The future of dentistry is more exciting than ever. It is a future in which the oral health care provider will be prepared to diagnose, treat, and ultimately prevent the entire range of oral health problems including oral infections, oral cancers, chronic orofacial pain, joint problems, salivary gland dysfunctions, and disorders of taste, smell, and swallowing and several others.

Mr. Chairman, the fiscal year 1995 request for the National Institute of Dental Research is $163,776,000. I will be very pleased to answer any questions that you may have.

[The prepared statement and biography of Dr. Harald Löe follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Dental Research

NIDR began the nineties with a Long-Range Research Plan that emphasized three major goals: to work toward the eradication of dental caries and periodontal diseases, to maintain the natural teeth for the lifetime, and to expand our research to address all the problems that affect the teeth, the mouth, the face, and the jaws. To achieve these goals we pledged our commitment to individuals and groups at highest risk for oral diseases and craniofacial disorders. These groups include many older Americans and "special care" patients: people whose oral health is compromised by disability or by systemic disease and systemic disease treatments, including people with AIDS, genetic diseases, and chronic conditions such as diabetes and arthritis, and the many people on multiple medications.

With respect to special care patients, NIDR is pursuing several recent advances on many fronts, ranging from the discoveries of the genes responsible for a number of hereditary diseases of teeth and bones, to promising new research on a salivary inhibitory factor against the AIDS virus, to new findings with regard to systemic diseases that affect oral health, and to new insights into conditions more common in aging, such as oral cancer.

Oral cancer research is benefitting greatly from the discovery of biomarkers associated with tumor growth or tumor suppression. These include the so-called cancer genes (proto-oncogenes) as well as tumor-suppressing genes, along with cell factors such as stress proteins, growth factors, and enzymes related to the spread of cancer. These studies have provided the rationale for the use of beta-carotene and vitamin E to reduce the risk of premalignant oral lesions from developing into frank oral cancer. Our scientists are now testing which markers may be the most useful and reliable in order to enhance the effectiveness of clinical trials of chemopreventive drugs. We are collaborating with the National Cancer Institute in two studies: one involves an evaluation of treatments of oral cancer in elderly patients; the second is a study of risk factors comparing a patient and control population in Puerto Rico, where the prevalence of oral cancer is high.

Many members of ethnic and racial minorities are at high risk for oral disease. Not only is their oral health generally poorer than that of the white majority, but they often lack access to care. To address these problems, the Institute is currently supporting six developmental grants for Regional Research Centers for Minority Oral Health. These centers involve minority dental schools or schools serving large minority populations in San Antonio, Washington, New York, Newark, Nashville, and Los Angeles. Now in their third year, the centers have launched a number ofstudies, including looking at lifestyle in relation to oral health; oral manifestations of HIV infection in minority groups; oral cancer (which affects blacks disproportionately); and the relationship between periodontal disease and diabetes among Hispanic populations. The developmental grants will be replaced by full-scale, 5-year research center awards in FY 1995.

It is of some interest that a number of the systemic diseases that reflect on the well-being of the oral cavity are more prominent in women than in men. Sjögren's syndrome, in which the salivary and tear glands are progressively destroyed, affects nine times as many women as men. The need to find better treatments for this devastating disorder has led to testing combinations of drugs: an agent to stimulate gland secretion, and a drug to decrease the autoimmune response. Our long-term goal is to understand how and why the glands are destroyed. Our efforts in FY 1995 will focus on certain immune cells that produce substances called cytokines, which have multiple effects on other cells. It now appears that one cytokine, interferon gamma, can stop salivary cell growth during turnover. Understanding that process could lead to the development of drugs to block glandular destruction and thus provide relief to thousands of affected patients.

Many bone and joint disease are also more prevalent in women, including osteoporosis, rheumatoid arthritis, and temporomandibular disorders (TMDs), conditions of pain and dysfunction in and around the jaw joint. In order to capitalize on the expertise at NIDR and other NIH components, the Institute has proposed that a multi-institute hard tissue disorders clinic be established at the NIH Clinical Center in FY 1995. This would create, for the first time at the NIH, a clinical research site where patients with debilitating, painful conditions of cartilage and bone could be studied.

NIDR is committed to furthering research on the temporomandibular disorders (TMDs), which women report twice as often as men. In some cases individuals have undergone surgery to place a joint implant--or to remove the implant in cases where it has failed. The Institute has long advocated conservative approaches aimed at restoring function and relieving pain, and will continue to support basic research to understand the causes and natural history of TMDs. One important result of this research has been the development of new research diagnostic criteria, using both physiological and psychological measures. Ultimately, using these criteria, investigators can effectively study surgical and non-surgical interventions.

We are also supporting several new initiatives to stimulate an expansion of TMD research. Principal among them is an International Workshop on the Temporomandibular Disorders and Related Pain Conditions scheduled for April 1994. This meeting, co-sponsored by the Office of Research on Women's Health, other NIH components, the Agency for Health Care Policy and Research, and the Food and Drug Administration, will bring together a world-class group of investigators to delineate the state of the science and develop a research agenda. Representatives from TMD patientgroups will also attend. These efforts and the expanded research agenda for FY 1995 are expected to yield improved patient and provider guidelines for the diagnosis, treatment, and prevention of TMDs.

At the basic research level, our scientists have noted a connection between female hormones and inflammation. Women suffer more inflammatory diseases than men, and these conditions are often worsened during pregnancy (e.g., the swollen, inflamed gums of pregnancy gingivitis and exacerbations of autoimmune diseases such as lupus). Now our investigators have evidence that the hormones, estrogen and progesterone, but not the male hormone, testosterone, increase the adhesion of white blood cells to the cells that line blood vessels. This is a critical step in the cascade of events that leads to the tissue swelling, redness, and pain of inflammation. Future studies to be supported within the FY 1995 budget will be aimed at understanding the ways that female hormones modulate the immune system and developing ways to counter unwanted effects.

In January of this year the Institute launched the National Oral Health Information Clearinghouse as a resource to aid the special care community. Patients and their families need information about their condition; practitioners can contact the Clearinghouse for comprehensive information to better serve these patients. Clearinghouse services include maintaining a reference database of all oral health information publications and materials, and producing and distributing patient and provider education materials. The service is accessible by computer, letter and telephone.

The transfer of research advances to the public and profession has been further advanced by a series of continuing education programs for dental practitioners, the most recent of which was held in Seattle in March 1994. We have included in these presentations a discussion of a new approach to the treatment of tooth decay. The new concept emphasizes caries as a bacterial disease--one that can be eliminated in its incipient stages by eradicating the bacteria and adopting sound dietary and self-care habits, including the use of remineralizing solutions--instead of considering caries merely in terms of a cavity to be filled. If a filling is necessary, we emphasize materials and methods that minimize the loss of tooth substance.

This new emphasis parallels major efforts to develop new and improved biomaterials. In part, this research has been stimulated by concerns raised about the possible toxicity of the mercury contained in the standard dental amalgam. While there is no scientific evidence that the amount of mercury used in fillings is harmful, NIDR-supported research has led to the development of a mercury-free dental filling. The metals are consolidated using processes called fast diffusion and cold welding, where the bulk of the consolidation occurs when the filling is placed. A Cooperative Research and Development Agreement has been negotiated with industry to commercialize the technology, and we expect to start clinical trials shortly.

Mr. Chairman, at the outset I mentioned the NIDR Long-Range Research Plan. I did not mention its title, but from what I have described, I believe we were justified in calling the Plan, Broadening the Scope.

The FY 1995 budget request for the National Institute of Dental Research is $163,776,000. I would be pleased to answer any questions.

HARALD LÖE, D.D.S.
Director, National Institute of Dental Research

Birthplace and Date: July 19, 1926, Steinkjer, Norway

Citizenship: USA

Education: Oslo University, Norway, D.D.S., 1952; Dr. Odont, 1961

Professional History: 1974-1982, Dean and Professor of Periodontology, School of Dental Medicine, University of Connecticut, Farmington. 1972-1974, Director of the Dental Research Institute and Professor of Dentistry, University of Michigan, Ann Arbor. 1962-1972, Professor of Dentistry and Chairman, Department of Periodontology, Royal Dental College, Aarhus. 1971-1972, Associate Dean and Dean-elect, Royal Dental College, Aarhus. 1966-1967, Visiting Professor of Periodontics, Hebrew University, Jerusalem. 1956-1962, Research Associate, Norwegian Institute for Dental Research, Oslo. 1960-1962, Associate Professor, Department of Periodontology, School of Dentistry, Oslo University, Oslo. 1959-1962, University Research Fellow, Oslo University, Oslo. 1957-1958, Fulbright Research Fellow and Research Associate, Department of Oral Pathology, University of Illinois, Chicago. 1952-1955, Instructor in Operative Dentistry, School of Dentistry, Oslo University, Oslo.

Honorary Doctorate Degrees: University of the Pacific, 1993; University of Helsinki, 1992; University of Detroit, 1990; Medical University of South Carolina, 1990; University of Toronto, 1989; Royal Dental College, Copenhagen, 1988; Honorary Professorship, Medical Sciences University of Beijing, 1987; University of Medicine & Dentistry of New Jersey, 1987; University of Maryland, 1986; University of Bergen, Norway, 1985; Georgetown University School of Dentistry, Washington, D.C., 1983; University of Lund, Sweden, 1983; Catholic University of Leuven, Belgium, 1980; University of Athens, Greece, 1980; Royal Dental College, Aarhus, Denmark, 1980; University of Gothenburg, Sweden, 1973.

Honors, Awards: Harvard Dental Medal, 1992; Meritorious Presidential Executive Rank Award, 1991; Charles A. Schlack Award, Association of Military Surgeons of the U.S., 1991; Award of Recognition, National Foundation for Ectodermal Dysplasias, 1991; The Donald C. Knapp Memorial Lecture, University of Kentucky, Lexington, 1991; Award of Distinction, Academy of Dentistry International, 1990; honored by His Majesty the King of Norway (Commander Royal Norwegian Order of Merit), 1989; U.S. Surgeon General's Exemplary Award Medal, 1988; Swedish Dental Society International Prize, 1988; Goldstein Lecture, Emory University, 1986; Member, National Academy of Sciences, Institute of Medicine, 1985; Benjamin J. Robinson Lecture, University of Maryland, 1985; Alfred C. Fones Medal for Outstanding Achievement in the Service of Humanity, 1984; International Award of the Friends of the University of Connecticut School of Dental Medicine, 1983; Lister Hill Memorial Lecture, University of Alabama, 1983; Daniel F. Lynch Award, Dental Society of Greater Waterbury, 1983; International Lecturer of the Year Award, Academy of International Dental Studies, 1983; Gold Medal, University of Ghent, 1982;

Centennial Award, University of California School of Dentistry, 1982; Award of Merit, Hartford Dental Society, 1982; Irving Glickman Memorial Lecture, Tufts University, 1979; William J. Gies Award, American Academy of Periodontology, 1978; Arthur Merritt Memorial Lecture, Baylor University, 1977; Certificate of Achievement, Connecticut Society of Periodontists, 1976; Massachusetts Dental Society International Award, 1973; honored by Her Majesty the Queen of Denmark (Knight of Danebrog), 1972; International Association for Dental Research Award for Basic Research in Periodontics, 1969; honorary member and elected fellow of scientific and learned societies here and abroad.

International lecturer; author of more than 300 scientific articles, three of which are Citation Classics®.

GRANT APPLICATIONS

Mr. SMITH. Dr. Broder, how many applications did you receive and how many were funded?

Dr. BRODER. Historically, we receive approximately 3,000 to 3,500 applications per year. It fluctuates some, dependent in part on the number of amended applications received. We expect to fund approximately 1,090 competing grants in fiscal year 1995.

Mr. SMITH. And how many of those 3,000 would you consider to be very worthy of being funded if you had the money?

Dr. BRODER. We don't like to see anything that is above approximately the 40th percentile go unfunded (i.e., superior in rank to the 40th percentile).

Mr. SMITH. How many would that have been?

Dr. BRODER. That would probably be another 500 or so grants, approximately.

Mr. SMITH. So approximately a thousand compared to 1,500.

Now, what happens to the researchers in those 500 that were not funded? Do they end up going, in some instances, to help the ones that are funded or what happens to them?

Dr. BRODER. You are raising a very important point, Mr. Chairman. We find that investigators do different things. Some investigators will send in competing applications again and try to take into account the critiques and criticisms of the peer review and attempt to improve their applications. In some cases, however, particularly for our younger investigators or new people getting grants for the first time, there are significant problems. And sometimes they can't get funded, period.

Mr. SMITH. Have you ever done a study to determine what happened to those?

Dr. BRODER. We can provide you with our funding analysis of what people do with time. I can't give that to you right now, but I will be pleased to give it to you for the record.

[The information follows:]

There are anecdotal reports on what happens to those applicants between the 20th and 35th percentile who submit excellent applications but do not get funded; however, we have not done a detailed study of those applications. Four years ago we initiated the Shannon Award to provide limited support for highly meritorious applications below the payline. Each year, we make approximately 100 such awards for exciting proposals that might become fundable with the benefit of a small award to generate additional data to strengthen their next application. However, this helps a very small percent of individuals in the excellent range. Many of the other applicants utilize the critique in the summary statement to resubmit revised applications. Of those who resubmit, 27.3% are successful in being funded.

Mr. SMITH. I think it would be valuable if we would know what happened to the researchers or investigators that were in those teams that were not funded, and this goes back to something that happened back many years ago, when we were shoving more money at NIH than it could use. In many instances, we were told by Dr. Shannon that we were breaking up teams before they had accomplished what they started out to accomplish. In order to put in new applications, in some instances universities were pushing them to do it. In other instances, it was just a natural thing to happen.

I think it would be valuable to us if we knew what happens to these researchers and investigators that are in these teams that are not funded. Could you shed any light on that?

Dr. VARMUS. Well, I think it is important to remember that many of the investigators who may not be funded in this case may have other grants. Most of our grant holders have two grants. We also know that there is a higher rate of success of reapplication. There is some tutorial advantage to going through the grant review process.

There are also many other means for being funded. I think the proper way to do this kind of study is to go to a number of academic institutions and ask in a cross-sectional fashion how people are being funded at a medical school.

This is an important area that you have raised, and I have been eager to have some of my colleagues in the extramural community take a survey with particular reference to the success of our training programs to see whether people who are being trained in biomedical science are finding adequate avenues for expression of what they have learned during their training period.

I don't think that the issue you are raising of groups being split up is the issue anymore. Most people who are new investigators are not the product of the division of research teams. Instead, they are new investigators who come through a training program and are trying to establish their own laboratories.

Mr. SMITH. Well, you get the gist of what I am asking.

Dr. VARMUS. Yes, I do. It is an important question and I will try to continue my quest to get information on this topic.

Mr. SMITH. Okay. Dr. Olden, what can you tell me about the same thing? How many applications did you receive and how many were funded?

Dr. OLDEN. Our program, obviously, is not nearly as large as Dr. Broder's. We funded 422 grants this year. Our success rate is 21 percent. So with more resources, clearly, there are grants that are worthy of funding.

Mr. SMITH. Well, will both of you, to the extent you can, parallel with answers to the questions that I gave you?

Dr. OLDEN. Yes, sir.

Dr. LÖE. We will be happy to do that, Mr. Chairman.

We receive about 400 grant applications every year. We fund about 100 of those. So you can see that we are close to a 25-percent success rate.

I agree with what Drs. Varmus, Broder, and Olden have said—that increasing the success rate to something like 35, 40, 45 percent would be in order.

RISE IN ORTHODONTIC TREATMENT

Mr. SMITH. I see. I have been curious—as you have indicated, obviously not as many people have cavities, not as many people have teeth pulled, not as many people have fillings as they used to when I was a boy, but a lot more of them have braces on their teeth, don't they?

Dr. LÖE. Right.

Mr. SMITH. Is that because the dentists need something to do or are there more people who need braces?

Dr. LÖE. The simple explanation is that young people want straight teeth.

Mr. SMITH. There are as many crooked teeth as ever, about the same?

Dr. LÖE. I have seen data that would show that about 40 percent of American youngsters are getting braces. Of course, many of them are for cosmetic reasons, others for more functional health-related reasons. National survey reports showed that about 15 percent of children and 30 percent of adolescents had severe or handicapping malocclusions for which orthodontic treatments were highly desirable.

Mr. SMITH. But there isn't any difference, generally speaking, in the need or the shape of the jaw or the number of teeth that are out of line or anything?

Dr. LÖE. We are not seeing any increase in such anomalies in the last 30 or 40 years. Increased use of braces is more a marketing issue.

Mr. SMITH. Yes. Okay. Mr. Porter.

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Broder, all of us appreciate your service to the country, and I am not going to hector you on the issue of falsified data.

Dr. BRODER. God bless you, sir.

BREAST CANCER RESEARCH INTEGRITY

Mr. PORTER. I understand you had a little session with Chairman Dingell on this subject earlier, so I am not going to repeat that, but I would just like to say what I said this morning. This a very, very serious matter. It bears on the faith that people have in NIH and NCI and in government in general, which is the most serious matter. And I wonder if you could tell us what changes you plan to make or are making at NCI to restore the integrity and protect the integrity of the research in the future.

Dr. BRODER. Thank you for the question.

We have taken steps that are unusual if not unprecedented, in the last few weeks. We have removed a major figure centered at the University of Pittsburgh, Dr. Bernard Fisher, from his status as a principal investigator on one of our largest and oldest clinical cooperative groups. Dr. Fisher has led that group since its founding for approximately 40 years. He has seen approximately five or six NCI directors come and go.

Also, we have taken the unprecedented step, at least from my point of view, of essentially seizing the clinical data files of the group and analyzing the data ourselves. We have established a special team of auditors and have created a new Clinical Trials Monitoring Branch within the NCI whose major function will be to audit and establish quality control mechanisms for our major clinical trials operations.

We have a number of steps that have been initiated, including ethics training sessions for all of the key individuals that participate in our clinical trials cooperative group programs. We have taken certain steps to change the conditions of NCI grants that are being issued, including to put grantees on notice that there are a series of steps that we will require whenever data irregularities or fraud becomes an issue.

We have put our reanalyses of the affected clinical trials in our computer databases so that anyone who has access to Internet or any of the related services can download the entire studies themselves.

There are a number of other steps that we have taken which I would be happy to elaborate for you now or for the record.

[The information follows:]

STRENGTHENING THE MANAGEMENT OF CLINICAL TRIALS

In order to improve and strengthen the management of NCI supported treatment and prevention clinical trials, the Institute has initiated a number of administrative and program requirements. As of April 12, 1994 these are:

1. The terms of awards of the Cooperative Groups are being changed to require immediate re-analysis and publication of trials affected by scientific misconduct. Groups will be required to provide NCI with immediate access to all data from any trials affected by scientific misconduct so that NCI contractors, staff, and outside experts can corroborate the results of the re-analysis and distribute them immediately, if necessary.

   In addition, the terms of award of National Surgical Adjuvant Breast and Bowel Cancer Project (NSABP) were revised on March 23, 1994, to require full cooperation with NCI in all aspects of the response to scientific misconduct.

2. NCI has placed NSABP probationary status and will require the Group to strengthen all phases of NSABP auditing activities, including requirements for on-site visits, timely reporting of audit results to NCI, establishment of clear criteria for pass or fail in audits, appointment of an executive officer for the operations office, and prompt re-analysis and revised publication of all trials affected by the misconduct case.

3. The NCI asked for a change in the principal investigator and Dr. Bernard Fisher has stepped aside. The University of Pittsburgh was requested to name an interim principal investigator and executive officer for its NSABP grants and was advised to develop a plan for orderly succession of leadership responsibilities at NSABP. The University of Pittsburgh has named Dr. Ronald Herberman, the Director of the Cancer Center at the University of Pittsburgh, to act as interim director. An executive officer, Dr. Donald Trump, has been appointed to oversee the daily operations of the offices of the NSABP. An oversight committee, composed of experienced oncologists, breast cancer specialists, and two consumer advocates, has been appointed, and the membership of NSABP has received information regarding the fraud case and the operational deficiencies of the Group.

4. NCI has taken possession of NSABP's computer data-file; analyzed the B-06 (breast-saving surgery versus mastectomy), B-13 and B-14 (adjuvant therapy) trials; disseminated the results to the public and to the membership of NSABP; and has initiated a government-run, on-site audit of key breast cancer trials conducted by NSABP. In doing so, NCI has confirmed the principle that the granting agency can demand, distribute, and disclose a grantee's data in response to pressing public health needs.

5. A new Clinical Trials Monitoring Branch has been created and Dr. Michaele Christian has been appointed Acting Branch

Chief. A quarterly report on all outstanding audit reports and ongoing actions to investigate and resolve missing or discrepant data will be prepared. An operations manual to guide NCI staff in their response to scientific misconduct is being developed and will include guidelines for investigation, securing of data by NCI, notification of journals that have published articles containing fraudulent data, standardized procedures for maintaining medical records, disciplinary and corrective actions, recovery of funds, and prompt publication of re-analyzed results.

6. An appropriate advisory group composed of extramural scientists and advocacy representatives will consider the current status of quality control and quality assurance activities in the Clinical Cooperative Groups and discuss and advise NCI regarding the issue of fraud and misconduct in clinical trials.

7. All Cooperative Groups are required to provide a yearly plan for audit of their members and to provide NCI with a completed audit report of each visit within six weeks of the date of the visit. (The Groups will be required to file a preliminary report, detailing any significant deficiencies, to NCI within 24 hours after the site visit is completed.) Electronic mail procedures will be established for this purpose. NCI will also explore ways of having institutional on-site, data-control personnel periodically communicate directly with the grantor. Failure to file the preliminary or final reports may lead to prompt suspension of funding for the Group member audited, and tardy reporting or any pattern of non-compliance with quality assurance procedures will lead to probationary status or suspension for the Group.

8. An ethics orientation and training regarding the conduct of clinical trials and data management will be required by NCI for all Cooperative Group members.

9. A meeting of key representatives for the Cooperative Groups was convened in Bethesda, Maryland on March 31, 1994. Several topics related to quality assurance and scientific misconduct were discussed. There is a clear sense among the grantee institutions that quality assurance and scientific integrity are mandatory components of our government-sponsored clinical trials process.

Mr. PORTER. Is Dr. Fisher implicated in the falsification of the data?

Dr. BRODER. No, sir.

Mr. PORTER. Or was he simply responsible for the project?

Dr. BRODER. No, sir. The removal of Dr. Fisher as a principal investigator from the cooperative group program, which has the initials NSABP, is not necessarily a reflection of our feeling that he has engaged in misconduct per se. He is not a respondent to any misconduct actions that I am aware of at this time.

Our concern with Dr. Fisher at this time has to do with his unwillingness or lack of responsiveness to our requirements for certain monitoring functions, proper reporting functions and to respond to our requests and admonitions to reanalyze the data and publish them promptly.

We also were not convinced that he was taking our concerns seriously about data monitoring and reporting issues to us in a prompt way. And so we felt it would be better for all parties if he no longer served as the principal investigator.

Mr. PORTER. Let me ask you the same question I asked Dr. Varmus this morning. Do you think that criminal penalties for intentional falsification of data are warranted and would help to prevent this kind of conduct in the future?

Dr. BRODER. Yes. However, I would note that the fraud that occurred, the fraud that we are talking about committed by Dr. Poisson at Hospital St. Luc, is in a foreign country, and, therefore, I am not sure the Attorney General's representative could easily reach that individual——

Mr. PORTER. I agree with that.

Dr. BRODER [continuing]. In a criminal proceeding. But we could use all the help we can get.

I would certainly be happy to talk to the Congress or any committees of applicable jurisdiction about what issues we face and what issues are faced in the sanctioning of those individuals who do terrible things and also to protect the government's interest in returning Federal monies. We don't pay for fraud, and we consider the use of appropriated monies for fraud a total loss to the taxpayers, and we want our money back.

Mr. PORTER. Can I ask a very quick question with a quick answer? The cover story from Time Magazine this week, it is on cancer.

Dr. BRODER. Sir, I don't think I have read it.

Mr. PORTER. Haven't seen it?

Dr. BRODER. I don't think I have read it. Can you give me a reprise?

Mr. PORTER. All right, I will withdraw the question. I wanted to ask you if it was an accurate article and what input you might have had to it.

Dr. BRODER. I will read it and respond for the record.

Mr. PORTER. Yes, that would help.

[The information follows:]

TIME MAGAZINE COVER STORY

You asked about the Time Magazine cover story of April 25, 1994, and at the time of the hearing, I had not read the article. Since then, I have had the pleasure of reading this long and interesting article on contemporary cancer research. Virtually all of the scientists mentioned in the article have received NCI support and many are working in NCI intramural laboratories. In essence, this article is a tribute not only to the National Cancer Institute, but to the Congress that has supported this research on behalf of the American people.

J. Madeleine Nash wrote and wrote well about a wide array of new, even as new as last week's Science magazine, genetic discoveries about how a cell is transformed into a malignant tumor and how metastasis occurs. It is exceedingly gratifying to see the complex and often very challenging research done by NCI-supported scientists interpreted so skillfully for the public. At the same time as the author reports the limited degree of progress that has been made in reducing cancer mortality statistics, thee is a clear picture of why it is so difficult to attack the cancer cell in order to prevent or treat cancer.

The author was able to do what we as scientists cannot: interview patients and show the importance of research for offering new hope to people who are suffering with cancer. For instance, the pancreatic cancer patient, mentioned on page 60 travels from Dallas to the NIH Clinical Center to receive a new customized vaccine. The doctors who attend him at the University of Texas Southwestern Medical Center were long-time NCI physician scientists. This dissemination of NCI physicians across the country has been an undersung part of the program and helps to ensure that any American can receive the best treatment for cancer.

The article addressed some of the most exciting new cancer research, such as an enzyme known as telomerase and a new gene referred to as the multiple tumor-suppressor gene or MTS1. It highlights the significance of angiogenesis, that is, the development of new blood vessels, first in nourishing a tumor as it grows and then its role in metastasis, all of these are introduced and their function explained. It is exciting to read of so many people who have made such landmark contributions, but who are better known by others who have labored in cancer research laboratories, and by and large, have been known only to their peers.

If there is a demur to be made here, it must focus on the excitement the article will generate. All experienced cancer researchers can cite previous landmark moments when it appeared that one or many cancers had been routed, only to find that important research tended to set the agenda for more research rather than for a true prevention or cure of cancer. We are making headway, we are changing the odds as Patricia Steeg, an NCI intramural scientist, said in the article. We are creating new experimental treatments, but they are still just that, experimental.

We are grateful for this article and for the coverage that Time Magazine has given this important area of basic and applied cancer research. Please forgive us if we are a little hesitant to say we have passed or even approached the top of the hill in understanding and treating cancer. Cancer has proven one of the most demanding scientific and human challenges and should never be underestimated.

DISEASE EARMARKS

Mr. **PORTER**. The budget requests a 5.2 percent increase or $108 million for the Cancer Institute. However, most of that increase is earmarked for breast cancer and for AIDS research. What portion of the increase is for non-AIDS, non-breast cancer research, and what type of increase does that represent in percentage terms?

Dr. **BRODER**. Of the $108 million increase, approximately 69 million is committed to breast cancer and AIDS. Therefore, when you take that out, we are talking about something like approximately a 3 percent increase.

Mr. **PORTER**. So, far below the 4.1 percent that Dr. Shalala said was an absolute minimum?

Dr. **BRODER**. It is below. That is correct.

Mr. **PORTER**. All right. Looking at last year, the President requested increased funding for NCI. However, he also earmarked substantially more funding for breast cancer research. What was the effect of the breast cancer earmark on your budget and how did it change the priorities which were identified by the Institute in its initial budget submission? In other words, in what programs did that require cuts or downsizing?

Dr. BRODER. We have had moderation of growth or less proportional growth for lung cancer, bladder cancer, colon cancer, liver cancer and testicular cancer, as the major areas.

FUNDING PATTERN

Mr. PORTER. Recognizing the importance of breast cancer research, is there a rationale or a justification, such as it has been underfunded in the past, to make up for the vast difference in funding for each new case of, let's say, prostate cancer, as opposed to each new case of breast cancer that these increases represent?

Dr. BRODER. It is my personal belief that we should allow investigator-initiated research as much freedom as possible to allow the genius of the grantee community, who in effect drive the major ideas that we deal with and are our best hope, to use their own best insights subject to peer review.

As I said in my opening statements, there are several discoveries that might not have been called breast cancer or ovarian cancer or uterine cancer or what have you, which have profound effects on the tumors. Basic research does have had profound implications for many tumors. For example, the genes for familial colon cancer are linked to endometrial ovarian cancer as well as colon cancer.

The new gene, which I described, on chromosome nine has cellular control functions and in fact probably is associated with a broad range of cancers, including melanoma and, specifically, breast cancer cell lines. The story could go on and on.

I feel it is very important for us not to second-guess where basic science will yield new knowledge. And I could give you the iron lung metaphor, which I think is on point. In the early 1950s it might well have been logical to build the best iron lungs that money could buy, to attempt to computerize them, and even to build portable iron lungs. But that wouldn't have really solved polio, and it took someone coming in who might not have even known what an iron lung is or how it works to develop a polio vaccine.

And I think we in the Cancer Institute would like to have that philosophy be part of what informs our research support. We don't assume that we know more than the grantee community, and we can't substitute for the inherent genius of the individual basic and clinical scientists who do their work.

NATURAL PRODUCTS

Mr. PORTER. Dr. Broder, can I ask you about the tropical plant collection initiative that I have been so interested in and you have been dealing with, please?

Dr. BRODER. Well, we are very proud of our whole commitment to natural products and natural product development. We have, in fact, worked with botanical gardens and have a collection, a very large collection of natural products.

We have also led the way in establishing memoranda of understanding and agreements with certain developing countries. The National Cancer Institute protects their interests, if you will, in the products that we develop from them. Insofar as we can, we will provide training opportunities. And, insofar as the law will permit, we will also try to make sure that some good comes to the country that gives us access to a tropical plant for medicinal value so there will be some commercial return to the country. We do not simply come in, take a product, turn it over to some developer and have the original country not have any role. This is a very important issue.

We have a number of products that emerged from natural product development. Taxol is a kind of natural product that comes from the bark of the yew tree and was a very successful program with the help of the Congress and this Committee. We were able to take that agent from a not very practical starting point to the point where it now is an approved drug by the Food and Drug Administration. And, indeed, the shortages that we initially faced have been resolved.

There are many other examples of this, the product conocurvone, which is being developed as an AIDS drug, and so on. So we are very happy and proud of our role in this area.

Mr. PORTER. Dr. Broder, may I just say one thing? That, often, we need to not just protect the country of origin of the plant, the material, we need to protect the indigenous people who may have developed the processes and identified that from their own country.

Dr. BRODER. I completely agree. And the indigenous people wish their children to benefit. That is the most important thing that they care about. And they wish to have their children draw the benefits of what we can offer. And often that can be in the form of educational and training and research development opportunities, which we do offer.

We are very sensitive to this issue. I can't tell you that we can act as an independent State Department, but we are sensitive to this issue, and we try to take these factors into account.

Mr. PORTER. Thank you very much.

Mr. Chairman, I have additional questions for Dr. Löe and Dr. Olden, but I will hold them for the second round.

Mr. SMITH. Okay. Mr. Stokes.

DIET AND MINORITIES

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Broder, what do we know about the relationship between diet and cancer today that we, say, did not know five years ago. I am particularly interested in knowing about a culturally sensitive conceptual model for dietary change in African-Americans that I understand has been undertaken at NCI.

Dr. BRODER. Yes, we are very interested in this area, and we have a cookbook, Down Home Cooking, which we have prepared, taking input from the community. And we would be happy to provide you with a copy if we haven't already done so.

[The information follows:]

DOWN HOME HEALTHY COOKBOOK

NCI has provided a copy of the *Down Home Healthy Cookbook*, a compendium of family recipes by Black American Chefs Leah Chase and Johnny Rivers, to Mr. Stokes under separate cover, as requested.

Dr. BRODER. We think there are a number of basic issues that are important to stress. We think that it is essential to have a balanced diet that has five fruits and vegetables per day.

We think that excessive meat consumption, especially meat cooked at high temperatures, may cause certain processes. We now know and have a very clear understanding that meat cooked at exceedingly high temperatures may contain heterocyclic amines and other products that can be carcinogenic in animals. This is particularly true for beef and pork. These products will not be formed with stewing or with microwaving, but do occur with broiling or other related ways of cooking.

We think that there is an important role for fibers and a number of micronutrients that should be there. We think there is an important role for reducing fat consumption. And we think there is an evolving role for certain types of vitamin supplementation, but I want to urge everyone to recognize that this is a complicated area. We do still have a lot more research to do.

Mr. STOKES. How about your NCI researchers, Doctor, are they allowed to actively participate in the conduct of this research? To what extent are they also collaborating with others in the field?

Dr. BRODER. They do both. We have a number of diet and nutrition studies. We have the five-a-day program that I mentioned to you. We have the polyp trial. We have the women's health trial, NCI staff participate in all of these.

We have a vanguard group within our own NCI that will help coordinate with the larger study that is being conducted out of the Office of the Director of NIH. And that vanguard study was expressly set up to reach African-American women and Hispanic women and others who might not normally have access to these large scale studies so that we would have a better and more culturally relevant way of bringing them into the larger studies.

We have a Cancer Information Service (CIS) to which we can refer people—which is available through CANCERFAX and other routes in English and in Spanish. These will help individuals get nutrition advice.

But the answer to your question is, most assuredly, our staff, both intramural and those who manage grants, are very involved in this.

PROSTATE CANCER

Mr. STOKES. Dr. Broder, what are we doing about prostate cancer? The American Cancer Society tells us that African-American males have the highest incidence of prostate cancer of any racial or ethnic group in the United States.

Dr. BRODER. Sir, they have the highest in the world.

Mr. STOKES. That makes it even worse.

Dr. BRODER. Yes, it does.

Mr. STOKES. What is your Institute doing to resolve this problem?

Dr. BRODER. We are attempting to approach this problem on a number of fronts.

First, we are trying to see whether there are appropriate interventions that can be used on a population basis. For example, whether transrectal ultrasound or PSA testing can, in fact, bring early detection and a reduction in mortality. And we have a large study, our PLCO study, which will have substantial representation from the African-American community.

We have a study testing finasteride, which is a special kind of hormone inhibiter. That study will be a large scale one, approximately 18,000 men, some receiving the drug and some receiving a placebo. And that study also will have a special outreach function to try to reach African-American men so we can learn whether there is a prevention that could be easily applied.

And, finally, we have a number of programs that are testing new drugs, suramin, phenylacetic acid, lovastatin, which inhibit pathways that ultimately lead to the anchoring of certain oncogenes on the cell surface. Those are also primarily focused in our intramural program and have a heavy representation of African-American men. So we consider this an important problem.

I am also pleased to inform you that the head of our Clinical Pharmacology Branch, who has a special interest in prostate cancer, is Dr. Ed Reed, who is a brilliant African-American pharmacologist.

Mr. STOKES. Are African-Americans participating in those clinical trials also?

Dr. BRODER. Yes, sir, we have special outreach for them.

We do that in a number of ways. We have a minority component to our Community Clinical Oncology Program, for example, which is expressly focused on attempting to recruit for prevention, treatment and diagnostic studies representatives from the African-American community and from the Hispanic community, and other underserved groups.

ENVIRONMENTAL JUSTICE

Mr. STOKES. Dr. Olden, many leaders in the environmental justice movement have been discussing your Institute's recent national Symposium on Health Research and Needs to Ensure Environmental Justice. Tell us, what was the result of that symposium?

Dr. OLDEN. The objective was to develop a research agenda collectively, that is, the Federal agencies that have part of environmental health science research, that is our agency, EPA, FDA, NIOSH, ATSDR and others—the Departments of Energy and Defense were also involved.

What we wanted to do was develop a comprehensive research agenda for environmental justice research, and we were using a somewhat different paradigm. We wanted to go to the communities that are affected at the outset and get them to buy into whatever efforts were undertaken. Because, as you know, if we design these programs from our offices or using expert scientific review committees, often communities, they aren't culturally sensitive, and communities won't accept the programs. So the objective was to design a research agenda.

It was a two-day conference, and we had a lot of input. And what we are doing now is putting together a position or white paper on the conference, and after that is complete what we will do is parcel it out among the Federal agencies to decide which one of us takes on different aspects of the research agenda.

Mr. STOKES. Doctor, when we talk about environmental justice, particularly as it may relate to low-income or minority populations, is there a special problem in the United States?

Dr. OLDEN. Well, the term has evolved. Originally, it started out as environmental equity. I think the correct term now, acceptable to everyone, is environmental justice.

I guess the implication was that regulatory laws are unequally enforced. That is a position that is held by many, that there are a number of regulatory laws on the books already that are unequally enforced.

However, above and beyond that, there are a lot of scientific issues. It is well-established that the poor and ethnic minorities are disproportionately exposed to environmental pollutants. But the scientific issue is whether those exposures are responsible for the disproportionate disease burdens that that population also experienced.

My guess is the environment is at least in part responsible. If we are going to get policymakers such as this panel here to allocate resources differently and change policy, health policy, we need a solid scientific basis to demonstrate that the disproportionate health status of the poor and ethnic minorities is, in fact, due to disproportionate exposure to environmental pollutants.

Lifestyle and access to health care clearly are part of it, but I think there are issues beyond one's control that has nothing to do with lifestyle, such as smoking and diet, alcohol and cigarette abuse.

Mr. STOKES. Thank you very much.

Thanks, Mr. Chairman.

Mr. SMITH. Mrs. Bentley.

DATA FALSIFICATION

Mrs. BENTLEY. Thank you, Mr. Chairman.

Dr. Broder, I am not going to dwell on the Montreal situation, but I am going to ask you one question on it. The doctor who falsified the breast research data in Montreal will not be eligible for NIH grants, we understand, for seven or eight years. Why isn't he permanently barred from receiving U.S. Government funds?

Dr. BRODER. He is, in my book.

Mrs. BENTLEY. But if you are not there, is there anything that can be done about that to make it for certain?

Dr. BRODER. We do not have the authority of debarment, to my knowledge. It has never been delegated to the level of the NIH. It is a departmental function. I cannot explain why eight years is the proper figure. Because, from my point of view, a lifetime bar would not be long enough.

Mrs. BENTLEY. So it would be up to the Secretary of HHS?

Dr. BRODER. I think it may technically be in the Office of the Secretary, but I believe this is done by in effect, a debarment board, which has its own function and has its own appeals process and so on. I don't believe this is a function that the Secretary would carry out at first hand.

Mrs. BENTLEY. Has Canada done anything to this man?

Dr. BRODER. The institution involved has removed him from a position of authority, but he still functions as a surgeon at Hopital St. Luc. However, he has lost the departmental status. He no longer heads a department.

The Food and Drug Administration did obtain a consent decree, if you will—that is what I call it; I am not sure that is what they call it—to bar him from ever asking for permission to use an experimental drug under U.S. Food and Drug Administration regulations for life.

CANCER IN MARYLAND

Mrs. BENTLEY. On another subject, this headline keeps popping up in our State of Maryland. It says, Maryland is second in the Nation in rate of cancer deaths. Delaware, which fits right into a glove in Maryland, is now number one, and the District of Columbia is up there above all.

What have we found in the environment—you talked about the environment a little bit before. But what is there that is creating this? Where are we on this research?

Dr. BRODER. I could take a stab at it first and then Dr. Olden can or would you prefer the other way?

Dr. OLDEN. Go ahead. Doesn't matter.

Dr. BRODER. We are looking at a broad array of environmental and occupational factors that could include breast cancer risk. We have a number of suspect agents in the environment.

For example, DDT or its product in the body, DDE, is an agent that we are focusing on to see whether there are correlations between levels of that compound and breast cancer risks. There is also an interest in what we call halogenated biphenyls that have been used for industrial purposes for a number of years.

There is a long list of things that individuals have suspected, but we still do not have a direct correlation or a direct proof. And there are contradictory results in the literature.

One of the reasons we are doing a Long Island breast cancer study and the mid-Atlantic study, which will include Maryland is to see if we can identify those specific risk factors.

We feel that there are a number of things, for example, hormone replacement therapy, the kind of estrogen replacement therapy which some postmenopausal women take, if used on a prolonged basis may contribute to breast cancer risk.

We are studying certain areas of the country, for example Triana on the Tennessee River in Alabama, where poor people were exposed to very high doses of dumping of DDT by the Olin Chemical Company into a river from which they fished. Therefore, they were exposed to exceedingly high levels by virtue of eating contaminated fish. And we are studying that area to see if we can get dose response relationships.

We are studying the State of Michigan where there was an accidental contamination of PBB through an inadvertent mix-up. Somebody put PBB in livestock feed, and the whole milk supply of the State was damaged in a brief period in the mid–1970s.

So we are looking at all of these issues, but I can't give you a definitive answer because there is no consensus in the scientific community.

ENVIRONMENTAL FACTORS AND CANCER

Dr. OLDEN. We are collaborating with the National Cancer Institute on a number of these studies. For example, the Long Island

Breast Cancer Project, in which we are collectively looking at biomarkers to try to identify what the exposures are on Long Island.

In addition, we are collaborating with the Environmental Protection Agency and NCI to look at the health effects of agricultural chemicals, not only cancer, but all the other health effects. And pesticide exposures in animal models is clearly one of the risk factors.

We are also looking at EMF, electromagnetic fields, as a possible cause for breast cancer. And we have a large intramural research program looking at the effects of chemicals such as PCB, DDT, and dioxins and others that have estrogenic activity.

We live in a milieu of chemical agents that are both natural and synthetic that have estrogenic activity, and if it is the cumulative exposure to estrogens that lead to breast cancer, then possibly some of these estrogenic agents in the environment are responsible.

And like Dr. Broder, we are looking at the genetic basis of susceptibility to breast cancer. We supported most of the research over the years on dioxin, and dioxin is a very potent carcinogen. We are looking at early response genes that are turned on and off. So we are supporting, I would suspect, most of the research on the agents that have estrogenic activity or that have been demonstrated to be carcinogenic.

And finally, we have identified at least 50 chemical agents in the national toxicology program, that have carcinogenic activity. What we are trying to do is develop biomarkers, often in both humans and animal systems, to see if we can figure out the mechanism by which these agents cause cancer, either through disruption of hormone mediated mechanisms or by altering gene function.

Dr. BRODER. If I could just briefly——

Dr. OLDEN. But like Dr. Broder, I can give you no definite answers, but there are a lot of activities in the area.

Dr. BRODER. If I could just briefly add, its not always what you might be exposed to. That is one aspect of the equation. But it might be there as a protective dietary or food product or something that has been withdrawn or is not being taken in in adequate amounts. There may be certain protective things in the diet and in certain types of foods that—genistine, for example, which is a product of certain types of soy products and so on, that might actually be protective and the lack of access to certain types of food products may actually provide a risk as well.

DIET AND CANCER

Mrs. BENTLEY. Well, this photo is in one of the news magazines this week, Dr. Broder.

Dr. BRODER. Looks like broccoli.

Mrs. BENTLEY. Yes, earlier you were talking about food. The title says: Are vitamins an effective tool in preventing cancer?

Dr. BRODER. Yes, we have funded a study on the product sulforaphane by Johns Hopkins, which is in broccoli and other cruciferous type vegetables.

Mrs. BENTLEY. You mentioned fish in the river down in Tennessee.

Dr. BRODER. It is the Tennessee River, but it is in Triana, Alabama.

Mrs. BENTLEY. I see. The people there have found that eating that fish has created a problem?

Dr. BRODER. Yes. There are a number of poor people, primarily African-American individuals, who live in Triana, and use the river as a food source. And when the company contaminated the river with very gigantic amounts of DDT, they were exposed to exceedingly high levels. We are trying to follow them and establish dose response relationships, to see if we can develop the cancer risk and also what preventions might apply.

We are also using a kind of a fish, the medaka fish, which is extremely sensitive to carcinogens. It is a small little fish but is extremely sensitive to carcinogens in the environment. And in collaboration with my colleagues at the NIEHS, this is turning out to be a potential model for many human carcinogens. If you will permit me, this would be to carcinogens what canaries used to be to miners who ventured into coal mines.

And so this is a fish that is extremely sensitive and you can very rapidly make certain determinations about whether there is a cancer-causing potential of a suspected chemical. This is a research project that we are doing collaboratively.

Dr. OLDEN. May I add, organochlorines accumulate in tissue. And they bio accumulate in fish tissue and as consumed by humans in doses that are high enough to lead to different cancers. And clearly it is a bigger problem certainly among Native Americans who fish in the Great Lakes.

Let me just add that out of 450 chemicals that we have studied in the national toxicology program, we have identified two at least that prevent the growth of induction of mammary tumors in rodents. So we are also looking at these two as possible chemo-preventive agents.

Mrs. BENTLEY. Mr. Chairman, thank you.

Mr. SMITH. Okay. Mr. Serrano.

ENVIRONMENTAL JUSTICE

Mr. SERRANO. Thank you very much. Gentlemen, it is always a pleasure to hear from you, although this is a tough subcommittee to be on if you are a hypochondriac. It can be very tough. Dr. Olden, I am very interested and pleased with your work on environmental justice and equity and the emphasis that you place on it.

My question to you is: In certain parts of this country, many of these arguments over the environment will end up being political arguments, as in New York City recently over where to place medical waste incinerators. At what point does your work, for it to be complete, have to delve into the political arena, if you will? And can you comment on the lack in some communities, some minority communities, of the political clout to impact some of these decisions? And have we in fact established that in some way the political clout or lack thereof of some communities plays a major role on who is exposed to what at what time?

Dr. OLDEN. Well, when I took over this Institute almost three years ago, it was clear that the health of poor people in this country may well be impacted by agents and factors that are beyond their control. I felt that the environment was an important part of that, and we need to empower the people that are affected to participate in the decision.

And it seems to me that if the government has a responsibility to provide the scientific basis for making those kinds of decisions, as to whether an incinerator should be sited in a given community, it seems that the Federal Government has the responsibility for generating the science on the health effects of those exposures.

The same with whether there are petrochemical industries or other polluting industries, we have a responsibility to go in, to do monitoring and exposure assessment, to determine the possible adverse health effects, and to provide the information for communities.

The big problem that communities are having around this country is that there is a lot of anecdotal information to suggest that these exposures that they are encountering are causing disproportionate pulmonary problems, cancer, birth defects, and a number of diseases. But there are simply no data anyplace to support it or refute it, with one exception, and that is in the case of lead poisoning.

In the case of lead poisoning, we know that the kids that are lead poisoned are the kids who live where the lead is. If you don't live where lead is, you don't get lead poisoning. But except for lead poisoning, there simply is no data. Everybody intuitively accepts, but I don't think that is adequate. It has not been historically easy to change public health policy or regulatory policy. I think even if all the regulatory laws were enforced, the same in all communities, there would still be the big problem of whether those disproportionate exposures cause diseases. So I think the science simply has to be done.

Mr. SERRANO. Sure, and I see your point. It might be that some of the political decisions are being made locally based not on fact, but on what some people suspect may be a problem.

Dr. OLDEN. Well, a lot of money today is being spent on regulatory compliance. And I think none of us object to the expenditures that should be in place. But the fact is, the science is not in place to make many of those regulatory decisions. And particularly as it affects minority populations or poor people. And, in general, decisions simply are being made in the absence of the science. So I think we need to generate the science to make the intelligent public health and regulatory decisions.

Mr. SERRANO. All right. Dr. Broder, I am sorry my other colleagues are not here to hear this, but your exchange with Mr. Porter prompts a question on an issue that may not be related to anything we are discussing now, but it may be related sometime down the line, pending some foreign policy decisions.

We who read Spanish read from Spanish journals in Latin America that the Cuban government and the Cuban health care system have developed all kinds of things over the last 30 years that merit looking at. We also read it in English from England and other places. Yet, there is a very politically strong community in this country that discounts that as just a lot of publicity that the Cuban government has put forth for years and there is no need to look at it at all.

CONTRIBUTIONS OF CUBAN SCIENTISTS

Based on your exchange with Mr. Porter on tropical plants and health and science—and I assure you, nothing that you say will be used on the Floor of the House to suggest that you mean we should lift the embargo or not; I won't use it in my defense of lifting the Cuban embargo, which I support—do you have any information, are there acceptable research data that indicate there might be some things happening in Cuba, not only in the health delivery system but in research and the way they deal with children's health care that we should be looking at, or that we should try to protect in any political and economic change that they may face?

Dr. BRODER. Thank you for the question. Science does not know political frontiers. And I think that the essence of science and the scientific method is to ask individuals irrespective of their creed or nationality to provide data and facts and to let the facts drive the decisions that are made. Anyone can have a hypothesis and then it must be tested according to scientific methodologies. And those methodologies are pretty much accepted, I believe, all over the world.

The issue that you raise about Cuba is very interesting. We have followed certain reports of products of the shark, for example, that might have value. And what I would tell you is that we will keep an open mind.

I believe the Office of Alternative Medicine is in fact studying certain issues based on Cuban research. The NIH is certainly open-minded and perhaps Dr. Varmus might be able to provide more information on this point. We have a scientist who was a former fellow in our program who actually is involved in some of the shark research issues and other things that we are talking about.

So I would tell you that we are keeping an open mind and we will look forward to a day when we can interact with scientists all over the world, irrespective of political considerations. I don't know if that responds to your point.

Mr. SERRANO. Well, it does, in a very cautious way. I know it is a very difficult issue. But, you know, we get reports about a life expectancy in Cuba as high as ours. We hear reports about an infant mortality rate as low as a western nation. We get reports that indicate there is a big gap between what they have done in health care and what many in Latin America have been able to do. Then we are told by many politically strong forces in this country that it is all publicity, propaganda, and we should not pay attention to it.

I think we need to know, because if there is a political change in Cuba, we will play a major role in it. There is no way we cannot be involved.

And I wonder to what extent we should look and say there are things that have to be preserved and things that don't have to be preserved. In the area of education, which I pay a lot of attention to, it is pretty much established now by the U.N. and other groups that they have a literacy rate of 94, almost 95 percent. So that is why so many kids in schools in Virginia and other places are sending them books and paper and pencils, because it is clear that they don't need teachers or knowledge, they just need the software to conduct their work.

I know that there is no frontier for scientists, but many people look to the comments you make in terms of how we deal with someone. You know, all we know about them is that they can field three baseball teams immediately. Past that, no one believes anything we have been told over the years. I think it is very important to know.

Dr. VARMUS. Well, I agree with your sentiments about the free exchange of information. Currently, there are some avenues of exchange, as I am sure you know. Last year, for example, there was an outbreak of what appeared to be a nutritional deficiency causing a loss of vision and neurological disturbance among some members of the Cuban population.

The NIH, in particular scientists from the National Institute of Neurological Diseases and Stroke, did go to Cuba to try to help develop an understanding of that epidemic. Also, American scientists have traveled to Cuba to interact with the Cuban Scientific Community. I myself have traveled to Cuba and visited the biotechnology institute there. There are interactions with Cuban scientists at a number of international meetings. There is information available describing a number of interesting things they have done.

Mr. SERRANO. Okay. We obviously have a vote going on. I am the only one who hasn't voted, so we will take a short recess and will resume as soon as the Chairman comes back.

Thank you.

[Recess.]

FLEXIBILITY

Mr. BONILLA. Dr. Broder, if I could go ahead and begin, I would like to begin by asking something that related earlier to what the Chairman was asking Dr. Varmus about overall at the NIH.

Is it a mistake for Congress and the President to identify specific funding levels for certain cancers? In other words, are you allowed enough flexibility?

Dr. BRODER. We would certainly like to be advised and informed by the Congress acting on behalf of the people as to what priorities the public expects of us. But as I tried to indicate in my opening comments and in other avenues, I think it is very difficult to predict where important scientific advances will occur. And it is extremely difficult for a central governmental agency to attempt to decide or second guess the inherent creativity and genius of the individual scientists doing their work.

A number of advances cited in my opening comments had to do with genes now linked to some disease and yet at the same time they have fundamental implications in many diseases that might not even have been the target of the original research undertaking. I think we need good science. Without good science, you can't make progress. To paraphrase Dr. Howard Temin, a very distinguished member of the National Cancer Program who died recently if there is good science, you can expect that there will be progress on a broad front, meaningful progress.

Mr. BONILLA. So the bottom line is that you feel like you do have enough flexibility? I am not quite clear on what your final answer was.

Dr. **BRODER.** I support the President's budget.

HISPANICS

Mr. **BONILLA.** So I guess that means you do feel like you have flexibility. Moving on, how much did NCI support for research and training activities and how much of that was targeted to Hispanic, in Hispanic areas? Because if I recall correctly, in 1992, it was a little over $5 million.

Dr. **BRODER.** Five million is approximately correct.

Mr. **BONILLA.** Could you update the subcommittee on the programs that focus on minorities, like the National Hispanic Leadership Initiative that you touched on in your opening remarks?

Dr. **BRODER.** Yes. We have a number of programs that are targeted toward minority groups, focusing on Hispanic populations. We have a cancer prevention awareness program for Hispanics, we have a smoking cessation program. We have an Hispanic leadership initiative which is expressly focused on developing community-based action. We have separate Hispanic databases in our SEER program to ensure that we are adequately sampling the cancer rate in diverse parts of the Hispanic and Latino communities.

As perhaps the Committee is well aware, there are different types, different kinds of Hispanic groups that have different needs that we in the Cancer Institute must meet. The population in New Mexico may have different needs than the population in other parts of the country, in Florida, et cetera. We have risk factors for cervical cancer in Latin Americans, we have an oral cancer program in Puerto Rico, we have consumer-based health communications research targeted to Hispanic populations, we have a Spanish version of CANCERFAX and Cancer Net, which are our information services.

You can call up and ask for certain types of documents related to cancer information and prevention, diagnosis and treatment, and if you have a fax machine, we will send you the information in Spanish. So that gives you a sampling of the types of activities that we consider very strong priority. And we have certain Native American population programs which, to some extent because of the geography, may have some partial overlap as well.

CHILI PEPPERS AND CANCER

Mr. **BONILLA.** Something related to that, there is a recent article in the newspaper about a study out of Yale University and the Mexican National Institute of Public Health that found people who eat hot chile peppers were 17 times more likely to have stomach cancer than those who did not eat peppers at all.

Coming from an area where it has often been a leisurely pastime to eat a jalapeno with every meal and it has always been a lot of fun to do that, this now has turned very serious if in fact these figures are accurate.

Are you familiar with this study?

Dr. **BRODER.** Yes, but what I would say is with any one observation, I urge some caution as to how one would interpret it. Gastric cancer and gallbladder cancer and certain related caners may in fact, in some of the Hispanic populations of this country, be elevated. We are looking and trying to identify factors that may be at work here. We are looking to see whether there are certain bacterial causes of cancer. Helicobacter, which is an unusual type of bacteria, may be associated with certain forms of stomach cancer. And Dr. Pelayo Correa, who was very interested in these issues, is helping us work in this area. So I would not throw away your jalapeno peppers quite yet.

I think that things can be true but not related, and I would keep an open mind about this problem. We are trying to look for relationships and etiologic factors, but I don't want to simplify it to one specific food product. I think that would not be scientifically appropriate.

Mr. BONILLA. So you don't believe there is any cause for alarm as a result of this study, from what you are saying?

Dr. BRODER. I do not—based on the information available to me, I don't think you can use the one study that you are talking about to make dietary decisions. Nor do I believe the authors themselves went beyond a general association. And I think we need to be cautious about this and not jump to conclusions. We will be happy to give you follow-up information as we may learn it, but I would be very cautious about this.

Mr. BONILLA. All right. We will continue to welcome people to the River Walk in San Antonio and enjoy jalapenos with a margarita.

Dr. BRODER. I think the American Society for Clinical Oncology is in San Antonio. I am looking forward to my walk along the water, and I will be enjoying jalapeno peppers

BETA CAROTENE

Mr. BONILLA. On another matter, you state on page 4 of your written testimony that the use of vitamin A-related agents like beta carotenes have been shown to be effective in preventing head and neck tumors. Of course the study that people are talking about right now that was released a few days ago showed that smokers that got beta carotene had a higher chance of developing lung cancer than those who can not take the vitamin.

And this was quite a shock, I think, to a lot of people who really started to rely on and this beta carotene boom that we have seen in the last couple years. What kind of mixed message do you think people are receiving out there now after this study?

Dr. BRODER. Well, I think the warning here is that in God we trust, all others must show data. And I think that basically we really need to make sure that we have a scientific method based on sound scientific principles that allow for the defense of recommendations.

I testified before Mr. Waxman, whose subcommittee was evaluating whether there should be certain types of controls on the commercial claims of vitamins and other nutritional supplements, and my testimony there was that we should give the consumer as much freedom as possible, but where individuals make commercial claims, they should be required to defend them on some scientific basis.

With respect to beta carotene, there are conflicting data in the literature and there are certainly data to suggest that there is a positive value for beta carotene against certain types of cancers and cardiovascular disease. But what we need to recognize is in the Finland study these were heavy smokers, extremely heavy smokers, and the take-home message is that beta carotene in that setting appears not to prevent the lung cancers that one would get associated with smoking. And if anything, there actually was an increase in the beta carotene arm.

We have other studies under way in the United States under similar conditions that will look for comparability of this answer. But we did feel the public should be aware of this fact and that the facts have to be taken into account and we need to stick to our results when they come out, even if we don't want them to come out a certain way.

Mr. BONILLA. Thank you, Dr. Broder.

ORAL COMPLICATIONS OF DIABETES

Dr. Löe, just a couple questions for you, if you would. As we know, diabetes is common among Hispanic populations. Could you elaborate on what studies NIDR is currently supporting to lower the risk of oral complications of diabetes in high risk groups?

Dr. LÖE. It is true that diabetes is a problem in some Hispanic populations in various parts of the country. We have one study involving Pima Indians, who have a high rate of noninsulin-dependent diabetes. About 40 percent of the adult population have diabetes.

Very severe periodontal disease is often called the sixth complication of diabetes. Many people with diabetes lose their teeth before they reach maturity. We have studied this population of Pima Indians over the last 10 years to obtain a better understanding of the pathogenesis of the disease as it presents itself, both from a clinical point of view and from a biochemical point of view.

We have instituted a program of treatment and prevention in the Pima Indians; in due time, probably 1 or 2 years from now, we will have data to show the extent to which we can modify this disease.

MINORITY RESEARCH CENTERS

We have another project going on in San Antonio as part of what we call the Regional Research Centers for Minority Oral Health. The health center and the dental school in San Antonio, along with the Hispanic population there, have collaborated on a major study of lifestyle and diabetes relative to oral health.

That activity is part of a planning grant, which will be competing for a full-scale center award in 1995. We hope they will be successful.

Mr. BONILLA. Does this mean that San Antonio would be probably in the final three?

Dr. LÖE. That will depend on the peer review process. We have issued the requests for applications, and the decision on funding will be made by the advisory council in the fall of 1995.

Mr. BONILLA. As you know, you can hardly find a more concentrated population of Hispanics in any area beside south Texas. I know there are other areas as well.

Dr. LÖE. That is right, and the research center and the community are making good use of that opportunity.

Mr. BONILLA. Thank you very much.

Mr. SMITH. Mrs. Lowey. Are you through, Mr. Serrano?

Mr. SERRANO. I just have one question for the record. I am sorry. I just wanted to place before all three gentlemen the following questions for the record, and I will look forward to reading the responses.

As you know, I raised questions with Dr. Varmus this morning regarding Hispanic hiring and promotion at NIH, Hispanic health research and Hispanics as biomedical researchers. I intend to follow up by asking each ICD Director that appears before this subcommittee to answer this series of questions for the record. You three are the lucky first ones, but others will not be neglected, I assure you.

First, I would appreciate each of you telling the subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within the Institute.

Second, what percentage of your budget is directed specifically at Hispanic health issues, with the understanding that much of your research will impact Hispanic health without being directed at Hispanics?

Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

And fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

And let me say, as I did this morning, that the questions are not meant to be unfriendly in any way. The Congressional Hispanic Caucus is extremely supportive of the work all of you do. We ask with the full understanding of special needs in our community, a need to know what is being done to meet those needs, and then the continuing desire to be as helpful as we can in this process to keep your work going.

Thank you, Mr. Chairman.

Mr. SMITH. Okay. Ms. DeLauro.

OVARIAN CANCER—CA125

Ms. DELAURO. Thank you, Mr. Chairman.

Dr. Broder, I understand that recently, there was a conference on ovarian cancer, and a panel of experts at the NIH recommended screening only for high-risk patients such as those with two or more close relatives with cancer.

As a survivor of ovarian cancer, I am interested in the ways that we can better detect or we can screen for this disease, and I would like to ask you a couple questions about the recent conference.

Why is the CA125 blood test so imprecise? And is there any possibility of refining this to make it more accurate as a screening test? If not, is there any research under way in finding a better screening test?

Dr. BRODER. Thank you for the question. We are in fact trying to quantify whether CA125 and transvaginal ultrasound can be used in a meaningful way to reduce the death and suffering from ovarian cancer on a population-based study.

We have what is called our PLCO study, which is enrolling very large numbers of men and women to test various screening approaches. For women, we will be testing whether CA125, combined with transvaginal ultrasound, can be an effective predictor for who has ovarian cancer, permitting an earlier intervention. And that is a randomized study.

The specific answer to your question is that the CA125 test, as far as we can tell, does show some fluctuations as part of the inherent variability of the test. And since ovarian cancer can often, particularly in its earliest stages, be essentially silent and not symptomatic, it poses a challenge for the doctors who are taking care of a woman who otherwise feels perfectly well, except for a laboratory abnormality, as to what the next step would be.

And, in fact, if one thinks that there is ovarian cancer in there, sometimes it requires an operation of some type, with attendant morbidity or side-effects or days lost from work or other issues that can come up. And so the committee—the consensus conference which was organized essentially at the NIH level, addressed these issues and felt that, at the present time, they simply couldn't recommend the test without more data, such as the trial we are doing.

However, I feel that there is a great deal of information which is likely to result from the Human Genome Project, as well as research that we ourselves in the Cancer Institute support. As we get better at identifying the genes that are predictive for certain forms of cancers, in particular ovarian cancer, we will be able to target certain women for more intensive evaluation and perhaps make better use of the tests that we already have.

For example, BRCA1, which is often called the breast cancer gene, could also be called an ovarian cancer gene. Dr. Varmus has very generously agreed to supplement and enrich one of our own requests for applications that will attempt to intensively sequence the gene by a number of technologies and precisely identify the gene which has been localized to a certain region of chromosome 17, we will have a very special intensified effort to bring closure as to which genes are there and to how we can use them.

We will be putting in approximately $2 million and I believe that Dr. Varmus is going to be providing an additional million. And this is a request for applications that will go out and that we expect to fund this year. So we hope that we can come back and give you certain types of genetic markers that will allow us to more intensively monitor and use our resources more effectively so we don't have these problems with false positives and false negatives.

Ms. DELAURO. I really am anxious, you know, to keep in touch on this issue and to get some sense of what the latest information and the data are. After the conference, it is understandable that there are women, fearful of cancer and ovarian cancer, who will demand the routine screening. And then you have got doctors who don't know any better themselves about what they ought to be doing.

What is it that doctors are unaware of about the effectiveness of CA125?

Dr. BRODER. Well, as I mentioned, there are two issues. There is a false positive and a false negative issue. There is a certain amount of inherent fluctuation in the test, just as part of the natural process of testing or the way the lab test is performed, and therefore, if the test comes back high and crosses some threshold, since there is no backup clinical finding, sometimes it is good to have a test where you can corroborate it by physical exam or how a patient feels. With CA125 alone there is often no corroboration to correct for false positives and false negatives.

In the case of very early ovarian cancer, you might not have that backup. So if all you are going by is a particular test, it would be like a possible abnormal radar signal. You are not sure if something is out there or not. And then once you are in that position, you might have to take what amounts to an actual look via an operation. An actual laparotomy might be required. And the one thing we don't wish to do is subject women who are otherwise completely well to procedures that they wouldn't otherwise need, because, as you know, this is a very difficult situation.

So I believe the consensus conference said that more research is necessary. And I can assure you that we have a study which is already launched that will allow us eventually to answer the question, not only of CA125 but transvaginal ultrasound, which is also another test which we hope can be used.

Ms. DELAURO. Well, it was my understanding that just in terms of a certain level of confidence building in this area, that the combination of the ultrasound and the CA125 was supposed to provide us with the data that was necessary. In my own case, when I was diagnosed with ovarian cancer, there was no CA125. It was seven years ago, so it was essentially through an ultrasound, after five months of trying to figure out what may be the difficulty.

But I was beginning to feel, as I say, better about the process that we had—these two efforts which were working—but, I was very disconcerted when reading about this recent information, that we are not there yet in terms of really being able to focus in on early screening and early detection.

Dr. BRODER. I hear your concern, and I am very sympathetic to it. I understand where you are coming from. We at the National Cancer Institute have a difficult challenge. We need to get a consensus among the professional scientific and clinical community, or to have a clinical trial that backs us up. We need one—hopefully we will have two. We need at least one of those two.

When we don't have a consensus and we don't have clinical trials to back us up, it becomes difficult for us to make specific recommendations. And that is the challenge that we face.

Ms. DELAURO. Thank you, Dr. Broder.

NATIONAL TOXICOLOGY PROGRAM

Dr. Olden, let me ask you a question, and then we are going to have to vote again. In the House report last year, the Committee expressed its concern that a reduced number of substances or mixtures had been tested through the National Toxicology Program, the NTP.

And the NTP has that track record, a proven track record of identifying chemicals or substances which are likely to cause some sort of a carcinogenic hazard. The Committee urged in the last go-round that at least 15 new studies be started in 1994.

Can you tell us today how many of these chronic studies have been started in this fiscal year?

Dr. OLDEN. Yes. As of today, we have started 14. And we clearly will add one or more during the course of this fiscal year. So we have reached the level, the number that you suggested.

Ms. DELAURO. That the committee suggested. Can you provide the Committee with the information for the record on the number of and the names of the chemicals, the substances that are being studied?

Dr. OLDEN. Yes.

Ms. DELAURO. You may have done this in the past—I don't want you to repeat the information—from 1990 to 1994 if you can let us know.

Dr. OLDEN. Actually, I would like to correct the record. During my tenure, the numbers have fluctuated for the past 10 years. Sometimes it was ten, sometimes it was 12, sometimes it was down as low as six. But I can say that during my tenure, the number has fluctuated right around the average for the 10-year period, except for this year, and indeed we have increased 15, as you directed us to.

Ms. DELAURO. Okay. If we can just have that information for the past five years on this effort, it would be terrific.

Dr. OLDEN. Right.

[The information follows:]

TOXICOLOGY AND CARCINOGENICITY STUDY STARTS

Studies to determine all the potential adverse health effects from exposures to environmental substances are of two types, comprehensive toxicologic examinations and lifetime carcinogenicity studies. The toxicology studies usually precede the carcinogenicity studies because the information obtained about toxicity and dose-response relationships aids in the design of the carcinogenicity studies. In 1994 toxicologic studies will be started on 10 substances and carcinogenicity studies on 4 substances. Fumonisin B1, a mold contaminant of grain with a very high priority for testing, will enter both toxicity and carcinogenicity studies in 1994. The number of tests performed in the last 5 years are as follows: Toxicity: 1990, 23; 1991, 11; 1992, 42; 1993, 20; 1994, 10. Carcinogenicity: 1990, 14; 1991, 10; 1992, 4; 1993, 9; 1994, 4.

NIEHS will start the following 14 studies in FY 1994: Toxicity: Anthraquinone; Benzyltrimethyl Ammonium Chloride; Carbon Disulfide; Fumonisin B1; Glycine +Benzyl Acetate Combination; Indium Phosphide; Magnetic Fields (EMF); Methylene Blue Trihydrate; Dibutyl Phthalate; Retinoid. Carcinogenicity: Chloral Hydrate; Fumonisin B1; Glutaraldehyde; Methyleugenol.

TELOMERASE

Ms. DELAURO. I have, Mr. Chairman, additional questions for Dr. Broder on something that I have been reading about called, and I don't know if I have the pronunciation right, Dr. Broder, telomerase.

Dr. BRODER. Good enough for government work.

Ms. DELAURO. Okay, thank you very much. But I will submit them for the record, if that is okay.

Mr. SMITH. Okay, whatever you want. We can stay two or three more minutes if you want to.

Ms. DELAURO. Well, maybe I will do that, then. Having read this announcement about—which seems exciting, this new enzyme which it says plays a role in the aging of cancer cells, the article said that it might be just two years before tests could be started on a drug that would block the enzyme in human cancer patients, therefore offering the possibility of targeting cancer cells without harming normal cells.

Is this, in your assessment, a significant finding? Do you believe that this is a promise of some significant breakthrough?

Dr. VARMUS. Well, I have read the investigation's paper outlining this research. I think of the paper as interesting science. I think the promissory note in the newspaper is somewhat premature.

Dr. BRODER. I would like to follow up by saying one of the things that I don't wish to do ever is issue a promissory note to this Committee that we can't redeem. There are many who have said the Cancer Institute has done that in the past, and I am not in the position of arguing with them.

We want to tell you things that we know are logical and will follow up to equal our promise. That article was covered in The Washington Post, I have met with representatives from the company that is involved in this research and so we have some familiarity with it. I believe that this is a kind of project in basic research. And I would be extraordinarily cautious about promissory notes that are issued on behalf of that one project.

Ms. DELAURO. Well, but will you be following up these studies yourself? Will you be doing research? I appreciate what you said, because when you read the newspaper, and that is the way most people get their information, or from the TV, you know, it gives——

Dr. BRODER. I think there is a lot of research, not only from the one company which has published on this area, but there is research in a number of laboratories. I believe that Dr. Varmus has done research or has some knowledge of this field, and, therefore, I would defer to him on this and many matters.

Dr. VARMUS. Thank you, Sam.

Dr. BRODER. Speaking from the National Cancer Institute's point of view, I feel that this particular work is at the level of basic research and we are very happy when the public has its imagination captured by a basic research agenda, and that is to the good, but I would be extremely cautious about promissory notes.

And yes, this will be part of our research portfolio, but I would be very cautious about accepting someone who says I am going to have a drug based on this or I will have a clinical trial based on this in such and such a time limit. I am very cautious about this and I apologize if it created unwarranted expectations on your part.

Ms. DELAURO. Well, thank you very much, Dr. Broder, Dr. Varmus, Dr. Olden, and thank you.

Okay. We are going to recess for five minutes. Mr. Porter is going to be returning from the vote. I am going to go try to vote.

[Recess.]

ACKNOWLEDGEMENT OF DR. LÖE'S SERVICE

Mr. STOKES. [presiding]. The Committee will come to order.

Dr. Löe, I would like to start with you. And in starting with you, I would like to reference a very nice letter that the Committee has received from the members of the National Advisory Dental Research Council, National Institute of Dental Research. The letter acknowledges the excellent leadership that you have given as Director of this Institute since 1983, in light of your impending retirement on June 1st of this year.

Without objection, I am going to ask that this letter be entered in the record at this point and be made a part of these proceedings. I would just like to also say I know that our late chairman of this Committee, Mr. Natcher, had very special affection for you and great appreciation for your services. I know that he would want me also to acknowledge the great service you have given.

[The information follows:]

NATIONAL ADVISORY DENTAL RESEARCH COUNCIL

National Institutes of Health
National Institute of
Dental Research
Bethesda, Maryland 20892

April 15, 1994

Honorable Neal Smith, Chairman
and Members of the Labor, Health and Human Services,
Education and Related Agencies Appropriations Subcommittee
2358 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Smith and Members of the Subcommittee:

We, the members of the National Advisory Dental Research Council of the National Institute of Dental Research, want to acknowledge the excellent leadership of Dr. Harald Löe, who has been Director of the Institute since 1983 and will retire on June 1, 1994. In the 11 years of his service he introduced initiatives and programs that enabled analysis of changing patterns of oral disease in America and demonstrated the continued effectiveness--and cost savings--of oral disease prevention programs. In the 1980s he oversaw the emergence of oral health research as part of mainstream biomedical research, contributing to the advances in genetics and molecular biology that have established the NIH as the world leader in biomedical research. New training and career development programs, targeted initiatives to address the most vulnerable members of the population, and the establishment of multidisciplinary research centers are among the many effective measures he has implemented to further the mission of the Institute.

During his tenure Dr. Löe elicited the advice of research investigators from around the country in the development of long-range research plans to serve as blueprints for the future. As Council members, many of us have assisted in these efforts. In turn, these plans helped crystallize programs to advance biomaterials research and biotechnology and address the oral health problems of the elderly and of "special care" patients--those whose oral health is compromised by systemic diseases and systemic disease treatments. Such disorders include diabetes, cancer, AIDS and a number of conditions prominent in women, such as temporomandibular joint disorders and Sjögren's syndrome. New regional research centers focused on the oral health of ethnic and racial minorities, as well as expanded efforts to increase the recruitment of women and minorities to careers in research, are further testimony to Dr. Löe's vision and leadership.

Today Americans enjoy the best oral health of any nation in the world, in large part due to the advances made possible by the NIDR--the third oldest institute of the National Institutes of Health. NIDR is unique in the United states and in the world as a Federal institution devoted to oral health research, research training, and the rapid transfer of advances to the public and to practitioners. Dr. Löe deserves special recognition for his promotion of science transfer. He has fostered the establishment of a National Oral Health Information Clearinghouse, implemented continuing dental education programs for care providers, and has been tireless in his personal communications through speeches and writings addressing dental educators, the research community, the practitioners, and the general public about advances in research and their impact on oral and general health. We who have worked closely with him over the years truly believe he exemplifies government service at its best and are unanimous in affirming that he has well and truly served the Institute in its mission, "to improve the oral health of the American people."

Sincerely yours,

The Members of
The National Advisory Dental Research Council

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Dr. LÖE. Thank you very much. I appreciate that.

Mr. STOKES. You are certainly welcome.

MINORITY RESEARCH CENTERS

I know, Dr. Löe, that the Institute is currently supporting six regional research centers for minority oral health. Can you tell us what progress has been made and what some of the plans are for the future with reference to these centers?

Dr. LÖE. As you know, Mr. Stokes, the purpose of these six planning grants is to establish a firmer base for research in the oral health of minorities, as well as to build the research infrastructure in minority institutions and schools that serve large minority populations. For the long term, we want to improve the oral health of minorities in this country. Three minority institutions are involved: Meharry, Drew, and Howard. The geographic areas include San Antonio, Los Angeles, Newark, New York City, Nashville, and Washington, D.C. These six sites are now working toward expertise and the development of capabilities for responding to a request for applications for a full-scale center award.

We have issued the request for applications, and we hope that all six current grantees will be responding. We have monies set aside for three full-scale regional minority centers in oral health research in the 1995 budget request.

In the meantime, we have seen some exciting research developing, particularly in terms of the very special characteristics of some of the minority populations in San Antonio that I was just discussing with Mr. Bonilla. We have other projects going on—both at Meharry and at Howard—that would specifically address oral cancer in African-Americans, and with periodontal diseases as part of lifestyle and the special circumstances of minority populations.

The development of this research capability will be tested, of course, in the application for the more well-rounded centers that are each going to be funded at a level of $750,000 per year, over a 5-year period. We hope that these activities will, in due course, have impact on the oral health of minorities.

SMALL GRANTS PROGRAM

Mr. STOKES. Dr. Löe, under the other research budget mechanism, the Institute has included funds to support young and minority research grants. Can you tell us a little bit about this particular program?

Dr. LÖE. Let me first mention another relevant mechanism that we have used extensively, called minority supplements. About 40 of these supplements to existing grants have been made over the last two or three years, in order to bring young minority scientists into the mainstream of oral health research.

The mechanism that you have just mentioned—which we call the small grants program, focuses on minority and women researchers who have pilot data or have start-up projects that are worthy of support.

We have supported the small grants mechanism over several years, but this is the first year that we have emphasized minorities and women in this particular program. Within a year or two, we will know more about its attractiveness to this particular sub-population of scientists.

GENETIC CAUSE OF BIRTH DEFECTS

Mr. STOKES. Doctor, in the congressional justification, you reference something called the homeobox family of genes. Are there major research initiatives under way in the area of genetic research on birth defects? Also, can you tell us something about what genes have been found that are associated with abnormalities in development of the head and face?

Dr. LÖE. We have identified approximately 1,000 genes that are related to the development and the maintenance of normal tissue relations in the skull, jaw, face, and teeth. Many of these genes govern the embryonic development of the skull, and some are very important in terms of synchronizing the processes as the bony parts try to meet and then complete the development of the head.

One of these genes that we have identified is called the MSX2, which is, as you say, a homeobox gene. These genes have to do with the developmental phase not only of human beings, but of all creatures we know. The particular gene mentioned is about 600 million years old but is still preserved and has very specific relationships to the full development of the skull.

A mutation in this gene leads to the closure of the bony parts of the skull too soon, thus creating a very severe problem in brain development called cranial synostosis. It requires major surgery and other adjustments in order to provide for normal brain function.

There are other genes that we have discovered that relate to the development of the teeth and that govern disease processes. Probably even more exciting is the discovery that almost every tissue response is governed by a genetic component. This is what Dr. Varmus talked about this morning—the molecular technology that is available today not only to identify genes but also to map and sequence them, and ultimately understand the molecular governance of tissue reactions and responses. These are very exciting times indeed.

In related work, we have been dealing with clinical disease in the oral cavity through gene therapy. As I leave the Institute, I believe this is going to be the next phase of dental research. There is no question in my mind that we are on the threshold of something very important and exciting. I will be on the sidelines but I will be watching. It is certainly going to be an exciting time.

Mr. STOKES. I can imagine that. Just looking through your justification, I see here that there is a 600 million year old gene which is responsible for birth defects. I understand that this gene is involved in assessing whether the skull fuses too soon.

Dr. LÖE. The same family of genes is involved—from the fruit fly to birds to man.

Mr. STOKES. Thank you very much, Dr. Löe.

Mr. Porter, I yield to you.

COST SAVINGS FROM DENTAL RESEARCH

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Löe, let me add my word recognizing your wonderful and long leadership at the Dental Institute as you look forward to your well-earned retirement, and thank you for your service to the country and indeed to all humankind, the kind of work that all of you do in serving people.

Let me ask first about the very proud entry that you have in the NIH cost savings book. Maybe you could describe—I am sorry that all the Members aren't here, because I think all of us ought to have this, all of it, in our minds. In fact, every Member of Congress should have all of it in our minds.

But could you describe how NIDR has contributed to holding down health care costs and how that might translate into supporting health care reform?

Dr. LÖE. First, I believe it was crucial that we did a complete inventory of oral health and disease in the child, adult, and senior populations of this country in the mid–1980s. Between 1985 and 1987, we surveyed about 40,000 children, 20,000 adults, and 6,000 senior citizens, all over the country.

With that base, we were able to document the need for oral health care, and also to put some economic parameters to the equations. An economist in the NIDR, along with economists in the Commerce Department, were able to develop an estimate of the total cost and the total cost savings over the last 10 years, the decade of the 1980s.

It turns out that the total dental expenditure for the Nation is approximately $40 billion a year. That is what patients pay over a 12-month period. For 1989, we could show that—with the reduction in cavities in children, the reduction in severity of disease in adults, and the beginning of reductions in toothlessness, and the corresponding savings in dentures, dental appliances and fillings—the savings amounted to approximately $5 billion a year.

This annual savings amounts to approximately twice the money appropriated to the NIDR throughout its entire 46-year history. But more important than these numbers, is the fact that we were able to show that these savings were directly related to advances in oral health science and the changes that had taken place in the management and prevention of oral disease.

In summary, we have shown a distinct connection between the activities in the research lab and the actual benefit to the Nation.

Mr. PORTER. So we are saving in terms of health care costs, every year, what has been spent in research over a 40-year period?

Dr. LÖE. That is right.

Mr. PORTER. And this is a message that we have to get out to the American people and to the people that are most involved in health care reform. Because here is where the most money can be saved. Over the long haul, it is just astounding how much money can be saved.

Dr. LÖE. There is a tremendous return on the money.

EFFECTS OF ESTROGEN ON OSTEOPOROSIS

Mr. PORTER. Let me ask you about the Dental Institute and its research on the benefits and risks of estrogen. How do these studies relate to osteoporosis and other diseases prevalent in women?

Dr. LÖE. We have conducted research on the female hormones, both estrogen and progesterone, over many years, as they are somehow also very much related to changes in the periodontal diseases during puberty, pregnancy and lactation, and at the time of menopause. At the same time, of course, we have been interested in the hard, or mineralized, tissues—teeth and bone. Consequently, our research covers osteoporosis and especially the role of estrogen and fluoride.

Fluoride should not be forgotten in the discussion of the possible relationship here to osteoporosis. As a matter of fact, there are data, quite recent data, that would indicate that the appropriate level of fluoride, not necessarily the level that we use for preventing tooth decay, would be beneficial to women at risk for osteoporosis.

But back to the estrogen problem, there is of course a discussion at the moment about the benefit of estrogen in terms of osteoporosis treatment. The clinical data are not quite obvious in terms of the beneficial effect of estrogen. Probably we will have to wait for the results of the women's health study that has been started by the NIH. Those studies will probably be more meaningful in terms of assessing the true role of estrogen in osteoporosis.

PAIN RESEARCH

Mr. PORTER. Can I ask you about pain research? You are the lead Institute on that. I wonder if you could tell us what we have learned in the last year. I asked you about it before, but I want to see what progress we are making.

Dr. LÖE. I appreciate your interest. The latest progress relates to two areas. First of all, we have pretty much mapped the circuitry from peripheral pain to the spine.

And then quite recently, we have been able to follow some of the reactions of the central nervous system and the brain using PET scans and radioactive tracers. With PET scans, we have been able to show in quite normal individuals that, by shooting a little amount of hot pepper under the skin, there is a tremendous reaction in the brain.

Our interest at the moment is trying to find what is really the central nervous system's involvement in pain other than the sensory part of it. But it seems to be much more than that. We are quite excited about the latest imaging data.

The other area I would like to talk to you about when it comes to pain is the TMD area, where we have a real enigmatic problem and have had for many years. As we speak, there is an international workshop going on outside Baltimore where we have 80 scientists from all over the world trying to come to grips with the issue of diagnosis and clinical management of the temporomandibular disorders. We expect much from that conference. We have a technology assessment conference on this topic in the planning for 1995. Overall, we have been working very hard to bring some order to a very disorderly and a very difficult area, for both clinicians and for patients.

I would expect that within the next 5 to 10 years we will see marked improvement and progress. I would appreciate it if you would keep tabs on what is happening, because, as I say, I will be on the sideline.

ORAL CANCER

Mr. PORTER. What progress have you made in identifying markers for oral cancers?

Dr. LÖE. Well, we have worked on oral cancers together with the National Cancer Institute. As Dr. Broder just said, we have a study going on in Puerto Rico where we know that oral cancer is more prevalent than on the continental United States.

Our assessment will include both the environmental and the lifestyle problems relative to these patients, as well as some of the oral viruses that may be involved. Human papillomavirus has been connected with the development of oral cancer. Within a year or two, we will have the data.

Also, we are using cells from the lining of the mouth, or from saliva, that could be used as markers for early abnormal development in the oral lining and oral mucosa. We are trying our best to use some of the abnormal signs that we see in the cells in predicting transformation to oral cancer. We haven't arrived as yet to that point, but I do think that the progress that we have made in terms of using saliva as a diagnostic fluid is very promising.

Mr. PORTER. Dr. Löe, thank you very much for your testimony. I want to lobby Dr. Varmus for a minute.

I think this is a very good beginning, very good beginning to getting the message out about the value of biomedical research. But I think we have got to get the attention of some of the major media people so they can get the story out and into the minds of the American people. And I hope that you will push that, because that is a story that really needs to be told and told forcefully.

ORGANIZATION OF NIEHS

I am going to ask my final question of Dr. Olden, if I may. Dr. Olden, in your testimony you mentioned several areas of research which will receive increased funding. Are these activities covered by the overall increase for NIEHS, or must you cut back on other ongoing work?

Dr. OLDEN. Well, since I have been there the past three years, we have made major changes in the way that the Institute runs. There were three divisions. We integrated those three divisions into one. We also eliminated certain laboratories and we did that so that we could utilize our resources more effectively.

Remember, talking about three years ago, there simply were not resources to do a lot of the new things that obviously the opportunity existed for us to do. For example, there are certainly new technologies and new challenges that we need to address and before we can ask Dr. Varmus for the dollars, we have to demonstrate that we are using our present ones efficiently. So we reshaped the research program to demonstrate that.

The new programs that are described in my testimony are programs that have been initiated by rebudgeting, or cutting back on programs that are not as productive as we think they should be based on peer review. So we just have to set priorities. That is the fact of the matter.

Mr. PORTER. That is what we have to do also. I agree. Thank you all, gentlemen, very much.

I will go vote, Mr. Chairman. I am done.

RISKS FROM ELECTROMAGNETIC FIELDS

Mr. SMITH. Okay. I just had one other question I want to ask you before we conclude this afternoon. Any or all of you can answer it, if you know.

What do we know about electromagnetic fields that we didn't know a year ago or two years ago?

Dr. OLDEN. Well, I will start, because we have the assignment in the Federal Government to address that issue. I think what we can say today is that there is a substantial body of evidence that is epidemiological in nature that demonstrates that there is an association, although the association is weak, between exposures to electromagnetic fields and certain kinds of cancers, cancers of the central nervous system, brain, leukemias and breast cancer in males. However, there is no laboratory or in vitro evidence to support the epidemiological studies.

We have been, for the past year-and-a-half, conducting animal studies. We are exposing rodents to electromagnetic fields EMF, and we have been trying to find biological plausibility, see if there is any possible biologic explanation for the cancers that are supposed to occur. I can say one of the explanations was that melatonin, which is produced by the body decreases, after exposure to EMF.

It turns out that we don't see that in rodents. So we are conducting controlled in vitro laboratory experiments both in tissue culture, as well as in animals, to see if we can establish a biological basis for the explanation. And to date, we have been unable to do that. Although we have a mandate to do this over a period of five years and we are in the first year, we were already supporting EMF research to the tune of about $4.5 million a year.

We will obviously be involved in this research effort to a much greater extent than we are now, but at the moment there is nothing that one can say definitively about whether it does or does not cause cancer.

Mr. SMITH. I know you can't say for sure, but do you think in a certain length of time you can say definitively?

Dr. OLDEN. Yes, we have put together an external Advisory Committee of experts in the field. We have identified research projects that should be done and can be completed in the period of the five years according to the legislation. We are certain in five years we can come back to you with a definitive answer.

Mr. SMITH. You will have a definite relationship, a measurement between certain kinds of fields and certain diseases or——

Dr. OLDEN. Yes, we are looking at cancer, birth defects, and the others that I mentioned. Most of these experiments are going to be done in animals and in in vitro using human tissue and organ systems, to see if there is any possibility that this could happen. Most of the work that has been done to date has been done by physicists, and there have been no interactions with biologists. The new thrust will involve the collaborative interactions, interdisciplinary programs.

Mr. SMITH. Do any of these studies mathematically compare people who live under high lines, for example, and people who don't, and——

Dr. OLDEN. Yes, there will be better control than that. That is the problem of epidemiologic studies. It is more or less self-reporting. There are reports where the wiring comes into the house or the proximity of a bedroom or a school to power lines, but there are other environmental factors that complicate the interpretation.

Mr. SMITH. Electric blankets and things like that?

Dr. OLDEN. Electric blankets, household appliances, and also along power lines where they used defoliants, are also problems. It is not clear if traffic patterns have to be considered. I would have to say that there is an association. The association is very weak. There are a lot of confounding factors that need to be taken into consideration.

Dr. BRODER. We are working with our sister institute in this regard and we will be looking at specific wiring profiles in the homes at various target areas. We are looking at signal corps men from the armed forces of the Navy and other armed forces where there may be exposure to certain electromagnetic fields as part of their line of duty. We are looking at cellular phones where there may be specific and highly focused types of exposure.

We are doing so at the request of another committee of the Congress and we will be attempting to correlate exposure by billing records, if they will be provided to us, because that will be a track, that will be an objective measure of how the phone is used. And so there are a number of issues that we are exploring that are quite parallel to what Dr. Olden said. And I think there should be information that can emerge, but these are studies that are already under way and we will have to let them get done.

Dr. OLDEN. May I add, in the case of occupational exposure, it is clear that utility workers or State troopers who use the radar guns are exposed to very high levels. In those cases, it is clear that there is an association, but we are talking about ambient exposures that people like you and I have, that is the question.

Mr. SMITH. Are there any positive effects from it? Are you looking at that, too?

Dr. LÖE. A couple of months ago, I read about a beneficial effect of electromagnetic fields; someone had used a low current electromagnetic field to detour some of the sensory mechanisms in pain. This was launched as a form of local anesthesia during dental treatment.

I have absolutely no data as to whether this is scientifically valid, but it is at least an anecdotal report of a beneficial effect. What that is going to amount to, I don't know; it remains to be seen.

Dr. OLDEN. I am not aware of any beneficial effects.

Mr. SMITH. Are any other Institutes working on this?

Dr. VARMUS. These are the two major organizations. I don't know of others.

Mr. SMITH. Okay. Thank you very much. That is all. Thank you.

[The following question were submitted to be answered for the record.]

NATIONAL CANCER INSTITUTE

NATIONAL CANCER PROGRAM

Mr. Smith. What is the status of the evaluation of the National Cancer Program that the Committee requested in 1992? We have seen the reports of various subcommittees on particular aspects of the Program, but not an overall critical evaluation.

Dr. Broder. The third and final phase of the evaluation of the National Cancer Program (NCP) is now being conducted under the auspices of the National Cancer Advisory Board (NCAB). An NCAB Subcommittee to Evaluate the National Cancer Program has drafted a report that includes advice on research, policy, administration, and resource priorities for the NCP. This early draft is being reviewed by outside organizations and individuals and their comments will be considered for incorporation in the final report. The final report will be presented to the Appropriation Committee in the fall of 1994. In consultation with the NCAB, NCI will consider the recommendations presented in the report in setting the priorities for future cancer research directions.

There are three phases of the evaluation. In the first phase of this evaluation, six panels of experts from around the United States identified advances in basic, clinical and applied cancer research occurring in the last decade. They also assessed the potential of this new scientific knowledge for preventing cancer, reducing morbidity and mortality, and improving survival and quality of life. Each panel prepared a report covering one of the following areas of research: Molecular Medicine, Mechanisms of Cancer Induction and Progression: Endogenous and Environmental Exposures, Cancer Prevention, Early Detection and Diagnosis, Cancer Treatment, and Cancer Control. The chairs of the six panels then developed a consolidated report which presents those advances with cross-cutting significance in the biology and etiology of cancer as well as particular advances with far-reaching impact on detection, diagnosis, treatment, control and prevention of cancer. This report also includes a statistical overview of cancer in the United States and a discussion of future challenges. Seven volumes comprise the *Measures of Progress Against Cancer* report.

The second phase of the evaluation was conducted under the auspices of the President's Cancer Panel (PCP) which monitors the development and execution of the activities of the NCP. During the past two or three years, the PCP has heard testimony about a number of issues of importance to the review of the NCP such as technology transfer, patient advocacy, childhood cancers, the role of voluntary organizations, cancer in minority populations, cancer and poverty, and women's health issues. Varying viewpoints on cancer research priorities have been sought from representatives from basic and clinical sciences including epidemiology and behavioral sciences, public health organizations, advocacy groups, other governmental agencies, and the lay public. Specific groups known to be critical of the research mission and achievements of the National Cancer Program were invited to speak and engage in a dialogue. The President's Cancer Panel Special Commission on Breast Cancer was chartered in 1992 to undertake a thorough study of the wide spectrum of issues especially related to breast cancer and to make recommendations for future research priorities. Their findings and recommendations have been published and are also being included in the evaluation process since they are relevant to many aspects of the NCP.

In the third phase, the NCAB Subcommittee to Evaluate the National Cancer Program was established to make recommendations based on the information collected in Phases I and II. This subcommittee consists of members of the National Cancer Advisory Board (NCAB) as well as individuals who represent cancer survivors, the pharmaceutical industry, private industry and academia.

The subcommittee reviewed the *Measures of Progress Against Cancer* report, summaries and transcripts from the PCP meetings and the report of the PCP Special Commission on Breast Cancer. They also heard presentations on the role of government agencies and health care providers in the cancer mission, and "chronic disaster areas." One of these meetings, "Evaluating the National Cancer Program: An Ongoing Process," received testimony from the six chairs of the Measures of Progress Against Cancer panels as well as from invited speakers who included proponents of alternative medicine approaches to cancer treatment, cancer survivors, and critics of the NCP.

BREAST AND PROSTATE CANCER RESEARCH

Mr. Smith. You are estimating that you will spend $324 million on breast cancer research in 1995, with only $58 million allocated to prostate cancer. Can this disparity be defended by measures of incidence, prevalence, mortality, or quality of life?

Dr. Broder. The magnitude of the impact of an individual type of cancer is, indeed, important in our funding decisions. But funding is also a function of scientific opportunity, which, in turn is partially dependent on developments in other areas of cancer and in bioscience in general.

For example, advances in genetics have over the years helped identify women who are members of families prone to breast cancer, and research with these families, in turn, has moved forward to the point where identification of a specific gene responsibility for familial breast cancer is in sight. Epidemiology studies including the study of persons born in one country who have migrated to another (so-called migrant studies) have been helpful in identifying risk factors for both breast and prostate cancer, although the studies have shed more light on breast cancer. On the other hand, epidemiology studies tell us that African-American males have the highest frequency of prostate cancer in the world, and considerable research has focussed on the underlying causes for the difference. At this point we are not as knowledgeable about the familial basis for prostate cancer as we are for some types of breast cancer.

Since 1986 the amount of research funding for both cancers has grown very rapidly as the research community has submitted increasing numbers of outstanding grant requests. NCI funding for breast cancer research has risen from $51.6 million in FY 86 to

$263 million in FY 94, and $324 million in FY 95. Similarly, over the same time period, NCI funding for prostate cancer research has risen from $9.5 million to $55 million in FY 94 and $63 million in FY 95. This increase has been, in large part, a function of the new opportunities afforded by the discoveries that have enabled a much greater increase in prevention-directed research to be initiated. Two such examples include the Breast Cancer Prevention Trial, studying the potential of tamoxifen to prevent breast cancer among high risk women (through the use of the cancer treatment drug tamoxifen) and a similar trial of the potential for the primary prevention of prostate caner through the use of the new drug Proscar (used to treat benign hypertrophy of the prostate). It is also important to note that advances in areas of basic research not specifically designated as directed to breast or prostate cancer research may have significant import for that research. We hear your concerns, and will try to keep the committee informed of new scientific opportunities in prostate cancer.

SECRETARY'S ACTION PLAN ON BREAST CANCER

Mr. Smith. Describe for us your Institute's role in the Secretary's Action Plan on Breast Cancer. Which of the recommendations from last December's conference are you responsible for administering?

Dr. Broder. The National Cancer Institute (NCI) has a major responsibility for the research recommendations of the Secretary's Action Plan on Breast Cancer. A major emphasis of the recommendations coincides with NCI's mission to support collaborative multidisciplinary research. Efforts are already taking place at NCI to expand basic, clinical, and epidemiological research on breast cancer through a wide range of mechanisms including interagency agreements and the SPORE program. For example, NCI is establishing an umbrella agreement with the Beltsville Human Nutrition Center of the U.S. Department of Agriculture under which collaborative studies will be conducted, including investigations into the role of alcohol in breast cancer, the influence of dietary components on hormone metabolism, and the effects of caloric restrictions on breast cancer development. In addition, NCI is working with the Centers for Disease Control and Prevention to assist in the establishment and quality improvement of a nationwide system of cancer registries. The Action Plan also includes the establishment of a national resource bank for collection of clinical materials from patients with breast cancer, women at risk and unaffected women. NCI is also working with the Agency for Health Care Policy and Research in issues such as guidelines for pain management and also screening for breast cancer.

TRAINING & RESEARCH

Another important area of responsibility for NCI within the Secretary's Action Plan is the development of new opportunities for training in research fields related to breast cancer. This includes expansion of the traditional programs such as the National Research Service Award, Research Career Development Awards, and Minority Investigator Administrative Supplements as well as the use of other mechanisms such as support of researchers in cross-disciplinary sabbaticals, extension of training support for postdoctoral fellows who agree to pursue research careers, and debt forgiveness for research professionals.

One of NCI's chief responsibilities under the Plan is to expand the scope and breadth of biomedical and behavioral research related to breast cancer. Foremost under this recommendation is the continued and increased support for investigator-initiated research. In addition, the Plan calls for support of health services research and studies that can help to determine racial/ethnic disparities with the total population in cancer burden and risk as well as receipt of services. Much of this work has already begun through collaborations with the National Institute on Aging and the National Institute on Nursing Research in a program to identify factors influencing delays in diagnosis, evaluation of extent of disease, and supportive care for women over 65 with breast cancer. NCI also collaborates with the Health Care Financing Administration in linking data to Medicare files for studies on patterns of care. The Surveillance, Epidemiology and End Result (SEER) Program of NCI has recently expanded to capture more information on cancer in minority populations.

The Action Plan calls for increased examination of the role of nutrition, exercise and hormones in the development of breast cancer. In addition, environmental exposures have been shown to possess estrogenic properties and their influence on breast cancer is currently under investigation. Younger women with breast cancer also face hormonal changes due to treatment along with tremendous effects on personal and professional activities, and a request for applications has been released in collaboration with the National Center for Medical Rehabilitation Research to support research directed at problems confronting younger breast cancer patients.

Other recommendations from the Action Plan involve research on behavior and treatment effectiveness, on coping with breast cancer, on psychosocial barriers to participation in breast cancer research, and on model systems for health care delivery for health care organizations. NCI currently is supporting research on the role of counseling in improving quality of life and enhancing adjustment to risk notification or diagnosis of cancer. A separate NCI program announcement has invited applications for studies to develop, implement, and evaluate organizational models for integrating cancer prevention and detection services into existing prevention and primary care services at community health centers, public health clinics, and public university hospitals.

The further development of partnerships with industry through Cooperative Research and Development Program Agreements (CRADAs) to speed the translation of therapies from the laboratory to the clinic is another recommendation of the Action Plan. Addressing the issues related to this, such as liability and application of the Orphan Drug Act, will require the direct involvement not only of the industry collaborators but, also of the Food and Drug Administration, Congress, and consumers.

DETECTION, TREATMENT, MONITORING

Improving breast cancer detection, treatment, and monitoring through basic, clinical and health services research is a special emphasis of the Action Plan recommendations. Studies on the use of biomarkers to define groups at risk and as prognostic indicators is continuing to expand as promising new discoveries are made. NCI is investigating markers in the breast epithelium as well as molecular genetic markers of susceptibility. At the same time, NCI plans to co-sponsor a request for applications with the National Center for Human Genome Research to develop and assess ways to deliver genetic counseling that include approaches to reduce the risk for test-related psychological harm, stigmatization, and discrimination. In addition, development of new technologies and the improvement of existing technologies for imaging breast cancer in its earliest stages is a priority. The continued follow-up of screening trials is an ongoing responsibility, particularly noting the needs of women ages 40 to 49 and those over 75.

The Action Plan includes specific recommendations to make clinical trials more widely available to women with or at risk for breast cancer, to optimize enrollment and improve compliance, to establish outreach to geographically distant women and participants in Medicare and Medicaid, to seek improved insurance coverage for clinical trials, and to involve consumers from under-represented populations in the planning and evaluation of clinical investigations. NCI has been working to assist investigators in accruing women from under-represented minority populations to its clinical trials and is establishing a working group to consider ways to help minorities enroll in clinical prevention trials. At the same time, NCI is supporting efforts to increase the number of minority researchers and community physicians involved in clinical trials and has been developing materials for educating and informing racial/ethnic minorities, low-literacy populations, and older women about breast cancer, as recommended by the Action Plan.

PREVENTION

The Action Plan calls for increasing research on the prevention and causes of breast cancer. This includes the expansion of NCI efforts in hormonal modulation and chemoprevention. Ongoing studies in this area include the Breast Cancer Prevention Trial with tamoxifen in the Community Clinical Oncology Program (CCOP) and a study of the effectiveness of Vitamin E, beta-carotene, and aspirin in preventing cancer and cardiovascular disease in 40,000 U.S. nurses. The tamoxifen prevention trial is the subject of substantial discussion. The risks/elements of this study are being re-assessed. NCI is collaborating with the other institutes of NIH in the Women's Health Initiative that will assess whether cancer, cardiovascular disease and osteoporosis can potentially be prevented or forestalled by dietary, behavioral, and drug interventions.

Finally in the area of research recommendations, the Action Plan calls for extending the scope, depth and applications of quality of life and psychosocial research related to breast cancer. Recent NCI-sponsored workshops have identified research opportunities for this area. In response, NCI has not only initiated collaborative efforts for younger women with breast cancer and begun work in counseling interventions for high risk and newly diagnosed subjects, it is supporting research to develop and validate quality of life instruments for cancer trials that can be applied to special populations.

INFORMATION DISSEMINATION

In addition to its responsibilities in breast cancer research, NCI is addressing several other areas of the Action Plan recommendations. In particular, NCI is working to ensure that research results relevant to breast cancer are applied in a timely fashion. Research to improve translation includes the use of focus groups, public and provider surveys, and pilot tests of messages. Each year the NCI's Cancer Information Service receives hundreds of thousands of calls from health care providers and the public on cancer therapy, diagnosis and prevention and distributes approximately 18 million pieces of printed information annually. Other resources for communicating advances in cancer include the CCOPs (48 community programs in 27 states) and the Minority-Based CCOPs (8 programs), the Cancer Centers Program, collaborations with state health departments, the leadership initiatives among the Black, Hispanic and Appalachian health professionals; and the Cancer Awareness Program. Through these programs, NCI establishes public and private partnerships, as recommended by the Plan, to share information dissemination and education efforts.

In the area of policy development, the NCI works with its advisory groups, researchers from across the country, patient advocacy groups and the general public to develop clear statements on the state of breast cancer research and to determine needs and opportunities for research. As health care reform continues, the NCI will advocate increasing support for research and for mechanisms to ensure the timely application of research advances in communities across the country.

DOD BREAST CANCER

Mr. Smith. Are you satisfied with the way the Department of Defense is spending the $210 million provided in 1993 for breast cancer research?

Dr. Broder. The Department of Defense is earnestly trying to develop a high-quality, coherent breast cancer research program within a tight timeframe. We are grateful for their professionalism. The program, especially most aspects of the scientific review of applications and priority setting with regard to funding decisions, has essentially followed the NIH paradigm, which in this case has been re-created. NCI has remained in contact with the program as it has developed because a member of the NCI staff serves as a member of the Integration Panel which is responsible for advising the DoD on the overall direction of the program and its investment strategy. The NCI Bypass Budget document has been influential in many ways.

The DoD has engaged the services of two contractors to assist in the development of the program. One contractor provides logistical assistance in developing a computerized database to track the grant applications received, setting up meetings, sending out correspondence, arranging for travel and teleconferences. The other contractor organizes the review of grant applications submitted for training, infrastructure support and investigator-initiated research projects. This involved identifying and engaging scientists to serve on 41 peer review panels, resembling NIH-type "study sections," appointing NIH-type Executive Secretaries, some of whom were retired NIH Executive Secretaries or other extramural program staff members, to oversee the study section meetings and prepare NIH-type "pink sheets" as well as review summaries for the Integration Panel and assign the 4,000 or so grant applications received to the appropriate study section.

As of this date, all grant applications have been reviewed by study sections, review summaries and draft pink sheets have been prepared, priority scores assigned, a wide variety of data has been entered into the data tracking file, and the Integration Panel has met and made recommendations to the DoD as to which applications for training and infrastructure support should be funded. At the next meeting of the Integration Panel, funding recommendations will be made for approved applications for support for NIH-type investigator-initiated projects with priority scores between 1 and 3.

While the performance of DoD's program management team and the logistical contractor has been excellent, the performance of the contractor responsible for management of the grant review process perhaps needs improvement. Members of the Integration Panel felt that the makeup and expertise of the study sections was not always optimal and the summary reviews provided to the Integration Panel members were sometimes late and/or inadequate.

Mr. Smith. How closely are they following the recommendations of the Institute of Medicine report?

Dr. Broder. Thus far the DoD appears to have adhered to the recommendations contained in the Institute of Medicine report. General Travis, who I understand has now retired, did an outstanding job.

LONG ISLAND AND NEW ENGLAND BREAST CANCER STUDIES

Mr. Smith. Tell us briefly how you are structuring the Long Island and New England breast cancer studies, as well as your estimates of their length and cost.

Dr. Broder. The two studies, the Long Island Breast Cancer Study Project and the Northeast/Mid-Atlantic Study, are addressing environmental and other risk factors and breast cancer in high-risk areas. Both studies are in collaboration with the National Institute of Environmental Health Sciences. Research in the Northeast/Mid-Atlantic study is well underway. The Long Island Breast Cancer Study has funded certain projects, and is prepared to fund others and is still in the planning stage for still other major research grants.

Six studies in the Northeast/Mid Atlantic Study have been funded for four years at an total annual level of about $1.6 million per year. Research at Yale University School of Medicine will address organochlorine compounds and breast cancer risk. At Mount Sinai School of Medicine studies will look at environmental and genetic determinants of breast cancer. Studies of environmental risk factors and breast cancer will be added to the on-going Nurses' Health Study at Brigham and Women's Hospital in Boston. Environmental and genetic issues in breast cancer will be studied at SUNY at Buffalo. Studies on electromagnetic fields, organochlorine compounds, and other environmental exposures in breast cancer will be conducted at SUNY at Stony Brook. The Johns Hopkins School of Hygiene and Public Health will look at environmental factors and breast cancer risk in Maryland.

COLLABORATION WITH NIEHS

The Long Island Breast Cancer Study Project is part of the overall NIH research approach to the causes and prevention of breast cancer. NCI is working with NIEHS staff and a group of selected experts on environmental breast cancer. A meeting was called to initiate cooperative studies and to begin the complex process of developing a set of protocols to address the measurement of environmental exposures, technology development and validation, and historical reconstruction of exposure in the Long Island population. Grantees will be collaborating with NCI and NIEHS intramural laboratory scientists and epidemiologists.

A case-control study of women with breast cancer, being conducted by SUNY at Stony Brook, in Nassau and Suffolk counties, was funded in September and is already underway as part of the Northeast/Mid-Atlantic Breast Cancer Study. This research has been extended as an essential part of the Long Island Breast Cancer Study Project, while other investigators are being peer reviewed. It is not yet possible to say specifically how many women will be included in this research, but NCI will certainly attempt to identify those who have developed breast cancer on Long Island within a window of time.

NCI is networking with federal, state, local agencies, and private companies. There are six NCI-designated cancer centers in the New York area that are a resource for the Long Island Project. They have joined to propose a cooperative research venture to be supported by NCI. All six centers have indicated strong interest in participation, including Cold Spring Harbor Laboratory on Long Island, but the Long Island project has commenced, and will not necessarily wait for proposals from these cancer centers. The Laboratory is devoted to basic cancer research and is located on the border between Nassau and Suffolk counties, and has conducted a number of public forums on breast cancer, and is expanding its breast cancer research program.

LONG ISLAND PROJECT STUDY DESIGN

The essential task is to answer the question as to why breast cancer rates are high on Long Island. A case-control study will be the key mechanism of the Long Island Breast Cancer Study. NCI was directed by the Congress to look at a number of environmental exposures with an eye to breast cancer risk. New technology will be developed to measure and analyze certain exposures, including airplane emissions. These assays are not simple. Additional biological markers of individuals' cumulative exposure over years are needed, so creative approaches have to be developed. Exposures from contaminated water, soil and air will be considered. Exposures include the pesticide DDT and its metabolite DDE; the agents used in the nematode program, dichloropropane and dichloropropene; the termiticide chlordane; hydrocarbons and metals in exhaust; solvents; PCBs and PBBs; various herbicides; and electromagnetic fields. The Long Island Study will map housing wiring, and measure household exposures to electromagnetic fields. As the detailed protocol is developed, attention will closely focus on those exposures that may be associated with estrogenic or antiestrogenic activity.

Highly technical new computer strategies for mapping geographic areas will be used to relate breast cancer cases, household residence patterns, and many environmental issues such as contaminated water and other potential hazards.

As planned, the Long Island Project includes a six-month first phase, a second phase lasting approximately two years, and a third phase of varying length for different objectives. The first phase is focusing on methodology development, recruitment of study participants, surveying area residents, developing collaborations and receiving input, and developing specific plans for a minority outreach program. The second phase will include continuing active participant recruitment, interviews, and specimen collection, laboratory analyses, and interim data analyses. The third phase will provide for continued recruitment and analysis of the various types of data collected, with the preparation of final reports. Relevant members of Congress have been informed that our goal is to provide an interim report at the 3-year mark, but the full study will take roughly 5 years. They and the community advocates on Long Island understand and accept this.

INFORMATION DISSEMINATION

Because this research grew out of the concerns of Long Island women with breast cancer and their friends and families, an active program of contact with the citizens' groups has been maintained. Representatives of the NCI/Long Island Breast Cancer Study will join in networks of community groups and information will flow in both directions.

NCI has a valuable resource in its Cancer Information Service (CIS) which offers information on cancer and cancer treatment via a toll-free 1-800-4-CANCER number. This nationwide service has regional offices and the Long Island area is covered by the CIS at Memorial Sloan-Kettering Cancer Center. Representatives of the CIS have been involved in all aspects of this research and the CIS

Outreach program will be expanded to work with Project staff and the Nassau and Suffolk County Health Departments.

In addition to the amount set aside for the Northeast/Mid-Atlantic Study, it is estimated that $1.8 million will be obligated in 1994 for the Long Island Breast Cancer Study Project and over $4 million in 1995.

MAMMOGRAPHY

Mr. Smith. Your Institute's recommendation to revise the mammography guidelines for women aged 40 - 50 has generated quite a bit of controversy. Can you state for the record the scientific basis for changing the guideline?

Dr. Broder. On December 3 the National Cancer Institute (NCI) issued a statement of fact regarding mammography - facts as we know them today. The statement was based on a workshop that reviewed all of the world's clinical trials of breast cancer screening and a nearly year-long effort that reviewed the workshop's results. This statement emphasizes that clinical trials prove that screening with mammography and clinical breast exam will reduce death from breast cancer for women ages 50-69. The trials show a reduction of about one-third in the death rate under regular screening at an interval of one to two years.

The trials to date, however, have not shown definitive results in women ages 40-49. NCI had expected that a recently completed Canadian trial, for which results were published in November of 1992, would provide clearer information on mammography in young women, but this was not to be. The results from this trial are controversial, although a recently published paper addresses many of the criticisms that have been leveled at that study. In any case, it is still early in the follow-up from that trial, and more definitive results may be available in several years. Our knowledge may change in the future, but we feel the facts as we know them for this important problem must be made available. In effect, the Canadian study did not give us the answer that mammography works in women under 50. A meta-analysis of other trials also failed to give us the answer. As a general rule, we feel we must share both positive and negative results with the public.

The NCI statement is based, in part, on a review of the trials by a panel of leading researchers. The clinical trials leave us with considerable uncertainty, and this uncertainty has polarized the medical and scientific communities. In the absence of definitive results or at least a scientific consensus, we feel it is difficult for the National Cancer Institute to issue a recommendation unequivocally for or against screening for women in their forties. We believe it is critical that women and health professionals understand these essential facts about screening:

(1) *Risks and benefits:* To recommend a screening procedure there must be a balance between risk and benefits that favors the benefits. For mammography there are risks for false positive results (an indication of cancer when none truly exists) and false negative results (an indication of no cancer when

cancer is present). Each of these outcomes has its own implications (described below). Another area of risk is in terms of radiation. A mammogram is an X-ray with a power about 10 times that of a chest X-ray. While this level of radiation is very low, we must consider the procedure to be, in a sense, invasive since the breast is exposed to some excess level of radiation and therefore to risk.

The decision to have mammography involves a balance between these various risks and the potential benefit from finding the breast cancer and seeking proper treatment.

(2) *The benefits:* The benefits from mammography are clear for women 50-69 for whom regular mammography at an interval of every one to two years will lead to a reduction in the breast cancer death rate of about one-third. However, rigorous evaluation through clinical trials has not shown, as yet, a reduction in breast cancer death rates for women 40-49. Therefore, when considering the risks and benefits for women 40-49, the benefit side of the equation must be considered uncertain.

(3) *False negative results:* For women in their forties, forty percent of breast cancers will be missed by mammography, compared with about 25 percent of such cancers for women in their fifties and older. These so-called false negatives can leave a woman with a false sense of security. It is essential that a woman discuss with her physician any changes she may notice in her breast.

(4) *False positive results:* For women of any age, there is a chance of a so-called "false positive" result in which the mammogram indicates that breast cancer may be present, but after follow-up testing, which may include a biopsy, it is determined that, indeed, no cancer was present. The minor scarring from a biopsy both on the skin and internal to the breast may affect the ability of mammography to detect cancers at that site when the woman is older and is, therefore, at higher risk than during her forties. At a first screening about five percent of women will have a false positive result and at follow-up screenings throughout the forties the percentage varies between two and five percent.

(5) *The chances of developing breast cancer:* It is important that the likelihood of breast cancer be accurately conveyed. For women in their forties the chance of developing breast cancer is about 1.5 out of 1,000 - that is, between one and two women out of a thousand will develop the disease each year in this age group. The overall chance that a 40-year old woman will develop the disease before she is fifty is about 1 in 64. This likelihood of breast cancer is less than many women imagine, but many will consider this risk high. I am enclosing a chart that outlines these probabilities. Women who, for example, have a mother or sister who has had breast cancer, will be at a higher risk. The multiplicative factor is called the relative risk and for women who have both a mother and a sister who have had breast cancer the risk is about twice that of average risk.

(6) *Why mammography may not be effective for women in their forties:* First, why do we feel mammography is effective in older women? Simply, mammography detects some cancers before they have a chance to metastasize. Not all cancers can be found, but enough may be found to give a one-third reduction in deaths. There is no question that mammography can find cancers in women in their forties, although it is not as effective in finding these cancers - that is, it misses more - than mammography in women 50 and older. Even though these cancers are detected early through mammography, this early detection may not change the course of the disease. (Again, the trials have not shown a reduction in death rate in those who are regularly screened.) The apparent lack of effectiveness may be due to five reasons.

- First, we know that mammography cannot differentiate the breast cancer tumor from the less fatty tissue (so-called dense tissue) of younger women. If the cancers can't be found they can't be treated.

- Second, we know that some of the cancers in younger women are different biologically than those of older women, and it may be that some of these cancers cannot be treated as effectively as cancer in older women.

- Third, it may be that a higher proportion of cancers found in younger women metastasize when the cancer is very small, before it is detectable with mammography. The primary danger from cancer is the possibility that some individual cancer cells will metastasize (spread) to a vital organ and lead to death. In such a case mammography will not be effective because the cancer, in effect, spreads very early in its development.

- Fourth, and in a sense opposite to the third reason, it may be that younger women have a higher proportion of cancers that grow slowly and seldom if ever metastasize. In other words, it may be that those cancers that can be detected through mammography in women in their forties are very unlikely to metastasize and therefore it does not make a difference in the death rate as to when they are found -- death from these cancers is unlikely. Please note the survival figures for breast cancer: about one-fourth of women who develop breast cancer will actually die of the disease.

- Fifth, it may be that mammography can reduce mortality in younger women, but the level of reduction is less than the trials can detect. The trials in the aggregate can detect between a 20% and 30% reduction in death rate. In other words, we have strong evidence from these trials that the effect is less than 20%, if such an effect exists. As of today, there is no consensus in the scientific community that such a reduction can be achieved by screening, although the trials do not rule out such a reduction.

To sum up the relevant facts: 80% of breast cancer occurs in women ages 50 and over, 15% in women in their forties, and 5% in women less than 40. Of every 100,000 women in their forties about 150 will develop cancer each year. If all are screened about 5,000 will have a false positive that will require further testing but result in no cancer. About 90 of the 150 with cancer will have their cancer discovered and treated. About 60 will not have their cancer discovered - at least at the screening. About 40 of these 150 women will eventually die of their disease; about 110 of these women will survive their breast cancer. To date we have no definitive evidence that screening women will reduce the death rate from the disease for these women in their forties.

We must underscore that for women 50 and over, screening will reduce mortality by about one-third. The fact is that we do not know exactly why mammography has not shown mortality reduction in younger women. Research is underway. But the fact is that *we cannot state that screening for women in their forties effects a clear balance between risks and benefits*. On the contrary, the risks are clear and the benefits are, as yet, unproven, and therefore a decision for or against mammography in younger women will need to be individualized.

Nevertheless, we are still striving for consensus. We are working closely with the American Cancer Society. We are looking to the results of a randomized trial in the United Kingdom. This issue is not closed.

Mr. Smith. Do you have any plans to reconsider your decision?

Dr. Broder. This uncertainty, and conflicting recommendations from different professional groups, make decision-making difficult. Those organizations that recommend screening for women in their forties include the American Cancer Society and the American College of Radiology. Those that recommend against screening include the American College of Physicians [the largest professional group of internists], the American Academy of Family Practice, and the United States Preventive Services Task Force. No country in the world recommends routine screening for women 40-49 except for the Canadian Province of British Columbia and a few counties in Sweden. We at the NCI are not recommending for or against mammography for women in their forties because we do not have the data to substantiate that such a recommendation would lead to a reduction in breast cancer deaths. In 1987, when we formulated our guidelines that made such a recommendation, we had preliminary, very suggestive results that there would be such a mortality reduction, but it has not been substantiated. As a science agency we need to share these latest conclusions with the public and with health practitioners; we do not oppose screening mammography if a women or her physician decides that it is the best course, as long as they have the facts. However, as stressed in response to your earlier question, we are continuing to maintain a dialogue with interested groups. The situation is not carved in stone.

STAFFING REDUCTIONS

Mr. Smith. You have been assigned one of the largest two-year staffing reductions at NIH. What management principles are you using to absorb this cutback?

Dr. Broder. The process of downsizing employment in cancer research has been a major management effort during the last fiscal year.

To accomplish these reductions, NCI used a combination of principles: attrition, severely limited new hiring, termination of 50 appointments to research training positions, and reductions in the number of hours worked by non-permanent employees. These efforts reduced full time equivalent workyear consumption from 2601 in fiscal year 1993 to projections of 2400 for fiscal year 1994 and 2331 in fiscal year 1995.

We are conducting a thorough review of position allocations and have established the general principle in NCI management that our flexibility to meet new scientific management and research opportunities depends on our ability to generate vacancies for re-allocation to new needs. We recognize that stability in the institute and ability to meet new needs depends on a continuous process of reviewing our intramural training programs and graduating a proportion of the trained researchers to academic research settings. This process will allow new candidates to enter the intramural training program. Our intention is that the scientific programs of NCI and cancer research institutions can continue to cross fertilize each other within somewhat more restricted personnel resource levels.

While we will maintain these principles in 1995, we do hope to be able to restore our non-permanent employees back to their original schedules. Many of these employees are in the Stay-in-School program and employment with NCI enables them to finish their high school and college degrees as well as providing an introduction to the work environment.

We hope that the Congress and the public will understand the special challenges NCI will face as a consequence of these FTE reductions.

COMPREHENSIVE CANCER CENTERS

Mr. Smith. After a period of stability, you are planning to increase by two the number of comprehensive cancer centers. In addition, you plan to award up to six planning grants to prepare candidates to compete for comprehensive center status. Why have you decided to increase the number of comprehensive centers?

Dr. Broder. NCI plans to increase by about two the number of comprehensive cancer centers because many of the cancer centers which are currently classified as clinical are working successfully toward building strength in the eight programmatic elements which must be fulfilled in order to receive comprehensive recognition. Comprehensive centers engage in a complete array of research including basic science, clinical investigation, and cancer prevention and control research. These centers also perform important outreach and education activities, including education of pre- and post-doctoral research scientists, information dissemination to the public, and information and education programs for community health professionals. Comprehensive cancer centers do basic research, clinical trials, and community service and outreach. The Congress has for many years emphasized the importance of these activities in our Centers Program. These comprehensive centers are highly visible in and critically important to the communities and regions in which they are located. We predict that more institutions will become successful in competing for comprehensive status in FY 95, and in a sense, this is cause for some satisfaction.

Mr. Smith. Does your long-range budgeting include funding for the additional centers that you will be pressured to award to those who receive planning grants?

Dr. Broder. We predict that four or five of the institutions currently holding planning grants will compete for Cancer Center support grants (CCSG) in FY 1995. This will make FY 1995 one of the most competitive years in the history of the program. While the NCI will maintain its commitment to generating greater geographic diversity with the Cancer Centers Program, this is a competitive program which depends on the evaluations of peer reviewers. The likelihood is that some of those institutions holding planning grants will receive CCSG's and that they will replace existing cancer centers in the competitive process. It is important to stress that the Congress has expressed substantial interest and support for the centers-planning program effort.

SPORES

Mr. Smith. The Director of NIH was quoted at a Cancer Advisory Board meeting as questioning the merit of the specialized programs of research excellence (SPORE) mechanism. Your Institute has used this mechanism extensively in the past few years. Are you reevaluating the role the SPOREs will play in your research portfolio?

Dr. Broder. The NCI believes that the SPOREs in prostate cancer, breast cancer, lung cancer and gastrointestinal cancer were evaluated for merit with the same rigor used for the traditional R01 investigator initiated research grant. No research project in any SPORE supported by the NCI received anything less than excellent to outstanding scientific merit. At this time, we have every indication that these "translational research" grants are conducting innovative research and achieving their initial goal of linking basic scientists and clinical researchers more effectively than other types of research grants. It is still too early to tell how these grants will impact on cancer in the future. As with any new program, Dr. Varmus is wise to ask for accountability and proof of performance. We expect to be in a position to truly reevaluate their role within four to six years. SPOREs will continue to play a limited, specialized, role in the NCI's research portfolio.

ASSIST

Mr. Smith. There was concern last year about funding levels for the ASSIST anti-smoking campaign. How much funding is the program receiving in 1994, and has this required any cutbacks in its scope of activity?

Dr. Broder. Although there was concern about ASSIST funding levels during the previous year, funding for FY 94 has been set at the originally intended level. The total funding for ASSIST in FY 94 is therefore $22.2 million and no cutbacks in activity have occurred this fiscal year.

CONSTRUCTION

Mr. Smith. Tell us your plans for the construction funding you have requested for 1995 and the process you will use to distribute it.

Dr. Broder. The $12.5 million in construction funds will be used for three classes of construction: extramural grants, maintenance of existing facilities, and intramural construction at Bethesda.

We will obligate $7.5 million for construction grants to increase vital research facilities used by cancer research groups at universities through the country. In addition, $2 million is to be spent on needed repairs and renovations at the Frederick Cancer Research and Development Center in Frederick, Maryland. The balance of funds will be utilized for the highly relevant facility needs across the spectrum of cancer research.

$5.7 million of the $7.5 million for construction grant awards is set aside for continued support of Proton Beam Therapy Center at the Massachusetts General Hospital. The balance of the extramural funding will be awarded to grant applicants from throughout the nation. The construction grants are awarded after a competitive, peer review grant application process. The construction work at both Frederick and Bethesda sites is based on a detailed evaluation of research facility needs and on impacts on research productivity.

In our extramural construction effort, we will give weight to research in women's health, minority research activities, and prostate cancer.

CANCER CONTROL

Mr. Smith. Your statute requires that you spend 9 percent of your funding on cancer control and prevention activities. Some groups are concerned that you define "control" too broadly. What types of research and education activities do you believe appropriately belong in this category?

Dr. Broder. The National Cancer Institute defines cancer control as "the reduction of cancer incidence, morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results."

The goal of cancer control is expressed in terms of the reduction of cancer incidence, morbidity, and mortality rates. The aim is to reduce these rates through thoroughly validated intervention methods. To give cancer control its required objectivity and to help research proceed most effectively, NCI has developed a strategic decision-making model of five sequential phases of an overall research process. The model comprises (I) hypothesis development, (II) methods development, (III) controlled intervention trials, (IV) defined population studies, and (V) demonstration and implementation studies.

Included in these five phases of research are programs in chemoprevention, and diet and nutrition. These areas of research are pursued through both extramural and intramural mechanisms with the aim of identifying specific chemical substances that demonstrate anti-cancer activity in humans. Ultimately, these substances may be prescribed for high-risk individuals through dietary supplementation. In terms of diet and nutrition, the program goals are to conduct research in nutritional and molecular regulation, prevention-related epidemiology, clinical trials, and nutrition studies; to identify and validate cancer-preventive dietary patterns; and to encourage and change the dietary patterns of the public through NCI's information dissemination channels.

Cancer control also includes the identification and evaluation of technologies for early detection, biomarker research, rehabilitation for cancer patients, and community-based clinical trials in cancer prevention, control, and treatment. The major goal of early detection research is to increase the effectiveness of early detection practices that can lead to a reduction in cancer morbidity and mortality. Also, emphasis is placed on applying the technologies for early detection into medical practice. Research initiatives are undertaken on new methods and approaches for early detection with the goal of extending this research to comparative trials in high-risk groups, as well as in other defined populations.

A component of cancer control is designed to identify the most effective strategies for bringing cancer prevention and control methods to the public, the public health system, and the nation's health care providers. It identifies and develops strategies to overcome the barriers limiting the full transfer of new scientific results to practice. It also fosters cancer control research across the country and works with state and local health organizations/agencies on developing cancer control plans for their regions and making maximal use of existing data on cancer. Research is directed toward the application of proven cancer control strategies to reduce the risk, incidence, morbidity, and mortality of cancer.

Additionally, the National Cancer Institute must also perform the functions of reviewing and auditing clinical trials. A portion of these costs are considered to be cancer control.

Lastly, cancer control research monitors the cancer burden on the population of the United States through the measurement of cancer incidence, mortality, and survival and the assessment of individual, societal, and health service factors that mediate these cancer measures both directly and indirectly. The ultimate purpose of cancer surveillance is to guide future programmatic and resource allocation decisions of the National Cancer Program.

The surveillance effort includes developing information and statistical analysis systems, such as population-based registries and national probability surveys, and conducting a broad series of studies focused on specific cancer control indicators.

Mr. Smith. Can basic science be included in control and prevention?

Dr. Broder. Basic research in cancer prevention and control is not supported by the cancer control line item in the budget. However, basic science research is part of the cancer prevention and control research portfolio. For example, chemoprevention is a novel approach to cancer control that seeks to inhibit neoplastic development prior to or during the preneoplastic period through pharmacologic, nutritional, or endocrinologic intervention. As such, chemoprevention provides a useful complement to therapeutic modalities in current clinical use, and may be particularly useful in the control of cancer in tissues for which therapeutic intervention is relatively ineffective.

Research in chemoprevention includes laboratory and clinical studies of chemoprevention agents, clinical nutrition studies, epidemiological studies, chemoprevention trials, and clinical studies. These distinct areas of research provide for the systematic progression from basic laboratory research, to clinical trials, and then to applications in the general population.

To select compounds more efficiently for in vitro testing, prescreening assays were performed. These simple, rapid assays provide information to help identify potential chemopreventive agents by evaluating several basic mechanisms thought to be associated with both the initiation and promotion process of carcinogenesis.

Basic research is being conducted on diet and nutrient-dependent mechanisms in carcinogenesis and cancer prevention. An understanding of these mechanisms may contribute to the design of dietary intervention trials and may identify novel dietary effectors for cancer prevention.

Other basic research activities include work related to the development of intermediate biomarkers for the early detection and prevention of cancer. For example, studies have recently suggested a role for tamoxifen and 13-cis-retinoic acid as chemoprevention agents for breast cancer and upper aerodigestive cancers (head and neck esophageal and lung cancer), respectively.

To date, information regarding the lowest possible effective dose, as well as the heterogeneity of drug metabolism in the general population, has not been established. NCI investigators are collaborating with pharmacologists at the Food and Drug Administration in a study to establish the optimal biologic dose of tamoxifen to permit interference with estrogen stimulation of breast carcinogenesis.

In another basic research example, a researchers are identifying and characterizing the mechanisms by which oncogenes function to transform cells. To this end, structure/function analysis have been performed on members of the *myc*, *jun*, and *fos* oncogene families and have revealed various structural aspects of these proteins which are necessary and sufficient for cellular transformation.

Mr. Smith. Are you having any trouble meeting the 9 percent threshold?

Dr. Broder. Setting aside a specific percentage of the NCI budget for Cancer Prevention & Control activities can present special challenges, depending on the total funds being made available to the institute. To the extent that the increase for the NCI is greater than the required growth in Cancer Prevention & Control the expansion generally can be accommodated without shifting of resources from other areas of research. The funding increase for 1995 will be aimed at many significant initiatives including an expansion of the Community Clinical Oncology Program, Smoking Prevention & Cessation activities, and dietary and chemoprevention studies. Emphasis will be directed toward underserved populations.

For FY 1995 the legislation requires that 9% of the total funds appropriated be directed to Cancer Prevention & Control. This compares with the 7% requirement for FY 1994. The dollar increase is $51 million and represents over half of NCI's requested increase for FY 1995. As you are aware, for the next fiscal year 10% of the budget is required to be directed for Cancer Prevention & Control.

Mr. Smith. Has it required significant funding shifts out of other areas?

Dr. Broder. The increase in Cancer Prevention & Control for FY 1995 has not required a redirection from ongoing activities. The President's request is sufficient in that the proposed increase can be accommodated within the total budget.

SPORE

Mr. Smith. What is the average cost of a fully operational SPORE in 1994 and 1995?

Dr. Broder. The Specialized Program for Research Excellence (SPORE) within the NCI cancer center program includes awards to fully operational SPORE institutions funded through the P50 mechanism as well as smaller awards to institutions to conduct feasibility studies to determine whether they would qualify to become fully operational SPORE institutions in the future. The average cost of an award to a fully operational SPORE institution is approximately $2.019 million in 1994 and an estimated $2.2 million in 1995.

COMMUNITY CLINICAL ONCOLOGY PROGRAM

Mr. Smith. Identify 1993-1995 funding for the Community Clinical Oncology Program and the Minority-based Community Clinical Oncology Program.

Dr. Broder. In 1993, the National Cancer Institute combined funding for the Community Clinical Oncology Program (CCOP) and the Minority Community Clinical Oncology Program (MCCOP) was $29.4 million. The Institute's estimate for this program is $37.4 million in 1994 and $39.9 million in 1995.

SEER AND ASSIST

Mr. Smith. Identify 1993-1995 SEER and ASSIST program funding.

Dr. Broder. The National Cancer Institute funded its SEER program in 1993 at $12.5 million. The Institute estimates SEER funding will increase to $14.2 million in FY 1994 and $14.9 million in FY 1995.

ASSIST, American Stop Smoking Intervention Study for Cancer Prevention, represents a collaborative effort between the NCI, the American Cancer Society, State and local health departments, and other voluntary organizations. The purpose of ASSIST is to utilize proven intervention strategies for the prevention and control of tobacco use and to continue the downward trend in smoking and tobacco use. In 1993, NCI spent $18 million for ASSIST. The institute estimates this amount to increase to $22.2 million in 1994 and $23.4 million in 1995.

CANCER INCIDENCE AND MORTALITY

Mr. Smith. Update the charts on p. 157-162 of last year's hearing volume pertaining to cancer incidence, mortality, etc.

Dr. Broder. The tables follow.

Table 1: Estimated New Cancer Cases in U.S. for 1981 and 1991[1]

	1981			1991		
Primary Site	All	<65	65+	All	<65	65+
Oral/Pharynx	26,600	15,054	11,546	30,800	15,669	15,131
Esophagus	8,800	4,096	4,704	10,900	4,058	6,842
Stomach	23,900	8,059	15,841	23,800	7,239	16,561
Colon/rectum	120,000	38,967	81,033	157,500	44,505	112,995
Pancreas	24,200	8,139	16,061	28,200	7,237	20,963
Lung/bronchus	122,000	56,080	65,920	161,000	59,168	101,832
Male	88,000	38,623	49,377	101,000	36,766	64,234
Female	34,000	17,178	16,822	60,000	22,366	37,634
Melanomas	14,300	10,833	3,467	32,000	21,484	10,516
Breast	110,000	61,928	48,072	175,000	91,100	83,900
Cervix	16,000	11,673	4,327	13,000	9,813	3,187
Corpus/uterus	38,000	20,449	17,551	33,000	14,680	18,320
Ovary	18,000	10,448	7,552	20,700	11,067	9,633
Prostate	70,000	14,331	55,669	122,000	23,110	98,890
Testis	5,200	5,102	98	6,100	5,974	126
Bladder	37,000	13,488	23,512	50,200	14,796	35,404
Kidney/Renal pel.	17,600	8,983	8,617	25,300	11,528	13,772
Brain/Other nerv.	12,100	8,285	3,815	16,700	10,749	5,951
Hodgkin's Disease	7,100	5,718	1,382	7,400	6,253	1,147
Non-Hodgkin's lym.	23,000	11,080	11,920	37,200	18,796	18,404
Multiple Myelomas	9,400	3,313	6,087	12,300	3,797	8,503
Leukemias	23,400	10,813	12,587	28,000	12,868	15,132
All Sites	815,000	368,030	446,970	1100,000	435,654	664,346

Table 2: Cancer Incidence§ for 1981 and 1991
(Cases per 100,000 persons)

Primary Site	1981 All	1981 <65	1981 65+	1991 All	1991 <65	1991 65+
Oral cavity/Pharynx	11.83	7.66	49.82	10.41	6.48	46.32
Esophagus	3.54	1.91	18.39	3.87	1.89	21.99
Stomach	8.76	3.49	56.86	7.60	3.05	49.19
Colon/rectum	50.92	19.50	337.70	46.45	17.70	308.87
Pancreas	9.33	3.70	60.69	8.65	3.02	60.01
Lung/bronchus	53.89	28.54	285.27	58.06	27.74	334.84
Male	84.50	38.97	500.07	79.69	34.29	494.01
Female	30.85	18.98	139.16	42.03	21.70	227.53
Melanomas	9.37	7.93	22.54	11.50	8.89	35.32
Breast	88.68	61.02	341.18	110.17	73.56	444.29
Cervix	9.01	7.60	21.88	8.26	7.26	17.39
Corpus/uterus	24.04	15.60	101.05	21.06	12.49	99.29
Ovary	13.23	9.26	49.53	14.98	10.23	58.26
Prostate	81.95	16.63	678.18	162.98	37.84	1,305.14
Testis	3.78	4.08	1.00	4.40	4.75	1.13
Bladder	16.69	7.11	104.18	16.69	6.54	109.27
Kidney/Renal pel.	7.21	4.28	34.00	8.77	5.02	43.00
Brain/Other nerv.	5.93	4.60	18.10	6.13	4.69	19.26
Hodgkin's Disease	2.72	2.42	5.47	2.77	2.66	3.86
Non-Hodgkin's lym.	11.23	6.22	56.96	15.05	9.14	69.01
Multiple Myelomas	4.02	1.66	25.56	4.43	1.81	28.40
Leukemias	10.28	5.58	53.19	9.51	5.59	45.34
All Sites	351.65	183.43	1,887.13	404.87	201.83	2,258.11

§ Rates are from the SEER program. They are based on data from population-based registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco. All rates are expressed per 100,000 and are age-adjusted to the 1970 U.S. Standard Population.

Table 3: U.S. Mortality - Deaths in 1981 and 1991[δ]

	1981			1991		
Primary Site	All	<65	65+	All	<65	65+
Oral cavity/Pharynx	8,506	4,012	4,494	8,277	3,436	4,841
Esophagus	8,082	3,563	4,519	9,967	3,662	6,305
Stomach	14,427	4,315	10,112	14,225	3,990	10,235
Colon/rectum	54,606	14,616	39,990	56,776	13,313	43,463
Pancreas	21,790	6,778	15,012	25,534	6,446	19,088
Lung/bronchus	106,389	45,429	60,960	143,620	47,388	96,232
Male	76,650	31,757	44,893	91,600	30,353	61,247
Female	29,739	13,672	16,067	52,020	17,035	34,985
Melanomas	4,931	2,896	2,035	6,451	3,187	3,264
Breast	36,479	17,858	18,621	43,582	18,603	24,979
Cervix	4,815	2,833	1,982	4,514	2,685	1,829
Corpus/uterus	5,883	1,746	4,137	5,925	1,372	4,553
Ovary	10,855	4,831	6,024	13,028	4,455	8,573
Prostate	23,370	2,673	20,697	33,563	2,937	30,626
Testis	425	378	47	366	330	36
Bladder	9,813	1,719	8,094	10,406	1,606	8,800
Kidney/Renal pel.	7,702	3,135	4,567	10,270	3,542	6,728
Brain/Other nerv.	9,382	5,548	3,834	11,952	6,279	5,673
Hodgkin's Disease	1,997	1,257	740	1,625	993	632
Non-Hodgkin's lym.	12,612	4,867	7,745	19,572	6,293	13,279
Multiple Myelomas	6,698	1,975	4,723	9,268	2,184	7,084
Leukemias	16,442	6,561	9,881	19,103	6,274	12,829
All Sites	422,042	157,578	264,464	514,636	159,868	354,768

[δ] Source: NCHS public use tapes for 1981 and 1991.

Table 4: Cancer Mortality$^{\delta}$ in 1981 and 1991
(Deaths per 100,000 persons)

	1981			1991		
Primary Site	All	<65	65+	All	<65	65+
Oral cavity/Pharynx	3.45	1.96	17.03	2.93	1.61	14.97
Esophagus	3.26	1.73	17.19	3.51	1.73	19.68
Stomach	5.62	2.09	37.84	4.68	1.83	30.73
Colon/rectum	21.09	7.04	149.38	18.35	6.18	129.47
Pancreas	8.55	3.28	56.61	8.45	3.02	57.95
Lung/bronchus	42.97	22.12	233.31	50.04	22.39	302.43
Male	71.67	32.63	428.03	74.46	30.12	479.22
Female	21.66	12.72	103.29	32.15	15.39	185.16
Melanomas	2.01	1.38	7.68	2.22	1.37	10.02
Breast	26.59	16.76	116.24	27.04	16.19	126.09
Cervix	3.59	2.64	12.32	2.90	2.19	9.32
Corpus/uterus	3.97	1.59	25.74	3.35	1.21	22.91
Ovary	7.82	4.50	38.13	7.92	3.97	43.98
Prostate	22.86	2.68	207.05	26.76	2.91	244.42
Testis	0.33	0.32	0.45	0.25	0.24	0.28
Bladder	3.70	0.82	30.03	3.23	0.75	25.88
Kidney/Renal pel.	3.09	1.53	17.30	3.53	1.66	20.66
Brain/Other nerv.	3.90	2.71	14.74	4.32	2.84	17.83
Hodgkin's Disease	0.79	0.57	2.81	0.55	0.40	1.95
Non-Hodgkin's lym.	5.00	2.35	29.22	6.50	2.80	40.20
Multiple Myelomas	2.63	0.96	17.87	3.05	1.02	21.56
Leukemias	6.55	3.21	36.96	6.38	2.87	38.38
All Sites	167.40	76.49	997.15	173.41	73.84	1,082.19

δ Rates are based on the NCHS public use tape of total U.S. Mortality. All rates are expressed per 100,000 and are age-adjusted to the 1970 U.S. Standard Population.

Table 5: Years of Life lost from Cancer, United States, 1991

Primary Site	Person-years of Life Lost (Yrs in Thousands)
Oral cavity/Pharynx	135
Esophagus	149
Stomach	200
Colon/rectum	754
Pancreas	352
Lung/bronchus	2,145
Male	1,262
Female	884
Melanomas	128
Breast	845
Cervix	112
Corpus/uterus	89
Ovary	228
Prostate	311
Testis	13
Bladder	115
Kidney/Renal pel.	159
Brain/Other nerv.	268
Hodgkin's Disease	44
Non-Hodgkin's lym.	317
Multiple Myelomas	125
Leukemias	342
All Sites	7,867

δ Rates are based on the NCHS public use tape of total U.S. Mortality. All rates are expressed per 100,000 and are age-adjusted to the 1970 U.S. Standard Population.

Table 6: Trends in Cancer Mortality Rates by Primary Cancer Site, Ages 65 and Under Percent Change, 1973-91

Lung (Females)	73.7
Liver & Intrahep	20.5
Melanoma	16.2
Multiple Myeloma	12.8
Non-Hodgkin's	11.0
Prostate	10.2
Esophagus	5.5
Kidney/Renal	5.0
Lung (Males)	-2.1
All Sites	-5.2
Brain	-5.4
Breast (Females)	-6.9
Pancreas	-13.3
Larynx	-13.5
Leukemia	-17.3
Colon/Rectum	-20.2
Oral Cav & Phynx	-22.4
Thyroid	-26.6
Urinary Bladder	-27.0
Ovary	-27.2
Stomach	-28.6
Corpus & Uterus, NOS	-38.9
Cervix Uteri	-39.6
Hodgkin's Disease	-57.8
Testis	-66.2

PROTON BEAM CONSTRUCTION

Mr. Smith. Identify the remaining annual construction costs for the proton beam facility and the annual operating costs once construction is complete.

Dr. Broder. The pending FY 1994 NCI construction grant will be $7.3 million in FY 1994, and it will be matched by $7.3 million in Massachusetts General Hospital (MGH) funds. The last construction grant will be for $5.7 million in FY 1995, and again, it will be matched by $5.7 million in MGH funds.

The MGH has estimated their annual operating costs to be $4.2 million beginning in 1998 when the construction is completed.

CENTERS

Mr. Smith. Identify the number, type and subject areas of research centers supported in 1994.

Dr. Broder. The research centers program includes two major components, Core awards and Specialized Programs of Research Excellence (SPOREs) awards. Within the Core component of the centers program NCI estimates funding 12 basic laboratory centers, 13 clinical centers, two consortium centers and 27 comprehensive cancer centers in 1994.

Within the SPORE component of the centers program, NCI plans to fund nine fully operational SPORE awards in 1994, four for breast cancer research, two for prostate, two for lung and one for gastrointestinal, which includes colorectal and pancreatic, cancer research. NCI is also co-funding three SPORE awards with NIDDK for O'Brien Urology Research Centers.

NCI will try to fund additional awards to institutions in order for these institutions to conduct feasibility studies to determine whether they would qualify to become fully funded SPORE institutions. The areas of cancer research funded through this mechanism include breast, prostate, lung and gastrointestinal cancer research as well as research in brain tumors.

LEUKEMIA, LYMPHOMA AND RELATED CANCERS

Mr. Porter. I understand that the NCI participated in a joint workshop with the Leukemia Society in January 1994. What were the conclusions of this workshop, and how will the NCI participate in interdisciplinary efforts that target leukemia, lymphoma and related cancers in the future.

Dr. Broder. The 1994 Senate Appropriations Committee report provided funding to develop a nationwide peer-reviewed program in leukemia, and encouraged nonprofit organizations to participate in the development, planning, and funding for these programs.

Over the years, leukemia research has continued to provide a template for key breakthroughs in both basic and clinical cancer research. Fundamental concepts regarding oncogenes and chromosomal translocations, growth factors, dose-intensive chemotherapy, bone marrow transplantation, supportive therapies such as infection management and blood product support and stem cell biology have all been pioneered in leukemia. Many leukemias are now curable as a result of these landmark studies. In turn, the knowledge generated by basic and clinical leukemia research is continuously being extrapolated to inform our basic understanding and clinical approaches to solid malignancies. Thus, the support of leukemia research is, in effect, the support of all disciplines of cancer research.

The Leukemia Society of America (LSA) and NCI jointly organized and hosted a Leukemia-Lymphoma Workshop in January, 1994 with two objectives: 1) consideration of selected basic and clinical research areas which suggest opportunities for novel interventions to complement traditional approaches and improve prevention, diagnosis and treatment of lymphohematopoietic malignancies; and 2) identification of appropriate funding mechanisms to support expansion of molecular knowledge and promote rapid translation of basic discoveries into clinical testing. Participants from the NIH intramural (National Cancer Institute, National Heart, Lung, and Blood Institute, National Institute of Environmental Health Sciences), governmental (Environmental Protection Agency, Food & Drug Administration) and extramural communities (including the National Marrow Donor Program) discussed the following areas: 1) Molecular Foundations; 2) Stem Cell Physiology; 3) Epidemiology and Prevention; 4) Secondary Leukemias; and 5) New Therapeutic Strategies Based on Molecular Targets.

NCI supports investigator-initiated research using current mechanisms and encourages extramural scientists to develop clinical research proposals. NCI does not recommend creation of specific leukemia centers; LSA officials agree. There are three new mechanisms recently developed by NCI (indeed, developed with leukemia research in mind) that are particularly well-suited to promote innovative basic and clinical investigation in the hematopoietic malignancies: 1) new clinical cancer research R01's (R29s) for investigators who have not previously applied for a clinical research grant (Request for Application); 2) new R21 grants for 2-year pilot clinical investigation (Program Announcement); and 3) small grants (R03's) to support pilot clinical trials (Program Announcement), with the potential for NCI to develop its own *ad hoc* review if there is a vigorous response with large numbers of grant submissions from the extramural scientific community.

LSA and NCI officials met again in April 1994 to discuss various options open to LSA regarding the use of LSA-solicited funds for leukemia-lymphoma research. With the recent availability of new monies, LSA has the ability to develop new funding mechanisms. LSA and NCI officials agree that a particularly high priority would be the sponsorship of young clinical investigators who are entering the arena of translational research. Applications would be streamlined, with the potential for using electronic mail as the modality for submitting the grant proposal. A special area of great research opportunity that could be fostered through such awards is that of environmental leukemogenesis, including the clinical and molecular epidemiology of leukemias and lymphomas. NCI would provide a number of support mechanisms, including information dissemination technology and announcements of LSA grant programs through the Journal of the National Cancer Institute. In addition, there is the possibility of developing an informal link for each young clinical LSA investigator awardees with an appropriate NCI Program Director who, in turn, would provide mentorship with respect to scientific oversight and education regarding the NCI granting process. Finally, NCI could also join with LSA in the sponsorship of a yearly conference for LSA's grantees that would focus both on scientific advances and grantsmanship issues.

PHYTOCHEMICALS

Mr. Porter. *Newsweek*'s April 5, 1994 article entitled "Beyond Vitamins" noted NCI's multi-million-dollar project to find, isolate and study phytochemicals. Exactly how promising is the research of phytochemicals, and what impact could research advances in this field have on cancer-prevention research?

Dr. Broder. Phytochemicals are a broad class of naturally occurring non-nutritive secondary plant metabolites found in vegetables and fruits that might explain why increased intake of these foods has been consistently associated with a reduced risk of certain cancers. Although beta-carotene and vitamin C have been suggested as the most plausible protective agents in vegetables and fruits, two recent clinical trials have failed to confirm linkages between beta-carotene and lung cancer and vitamin C and stomach cancer, which were presumed to exist. There are various mechanisms whereby non-nutrient constituents of vegetables and fruit might inhibit carcinogenesis. In rodent studies of experimental anticarcinogenesis, it has also been shown that the dietary administration of vegetables, or chemical components of vegetables, protects against chemical carcinogenesis. Evidence also exists for components in fruits and vegetables which convey anticarcinogenic activity.

A number of epidemiologic studies are underway to evaluate the role of non-nutrient constituents in vegetables and fruits, such as phytochemicals, in analyses of dietary data. In addition, selected studies are measuring directly phytochemicals in urine collected from cases and controls. Since the current methodology for measuring these substances in urine is expensive and time-consuming, attempts are being made to develop laboratory techniques more appropriate for the large number of samples collected in epidemiologic studies.

Epidemiologic studies have shown that populations who consume increased quantities of fiber-containing foods have lower incidence rates for some types of cancer. An increasing number of naturally occurring non-nutritive components present in vegetables, fruits, and cereal grains have been found to inhibit carcinogenesis in laboratory animals when fed in a purified form and at pharmacologic levels. Studies are ongoing to develop analytical methods for the identification and quantification of these constituents in plant foods and to determine their biological activity, absorption, metabolism and mechanisms of action. Other studies are being conducted in animals to determine whether dietary fiber per se or other constituents in fruits and vegetables will inhibit mammary carcinogenesis.

Anticarcinogenic activity has been demonstrated in vitro and in animal studies for a highly diverse group of naturally-occurring chemical compounds including various forms of vitamin A, carotenoids (pre-cursors of vitamin A), and plant chemicals (phenols, isoflavones, and hormones).

The ability to prevent cancer is an overall goal of all of NCI's basic and clinical investigation. The development of pharmacologic, nutrition, and endocrinologic interventions to inhibit or delay the process of carcinogenesis is among the highest priorities of the Institute. Chemoprevention research consists of three components: 1) preclinical studies to investigate the cancer protective properties of specific chemical substances; 2) studies of the effects of chemoprevention agents through epidemiologic investigation; and 3) the clinical investigation of potentially active agents in Phase I, II, III clinical trials. Such chemoprevention interventions may also complement therapy or control measures in tissues where malignant transformation has already taken place and for which therapeutic intervention is relatively ineffective. The cross-cutting research necessary to move the discipline of chemoprevention forward, both in the laboratory and the clinic, is being designed and implemented by multiple NCI-supported institutions.

GENE THERAPY

Mr. Stokes. Gene therapy appears to offer tremendous hope for making significant progress with respect to the treatment of cancer. What progress has been made thus far? What opportunities for further advancement are on the horizon? To what extent will these opportunities be pursued at the FY 1995 budget request level?

Dr. Broder. Important new findings involve the successful cloning of three distinct genes that encode melanoma antigens recognized by tumor infiltrating lymphocytes (TIL). The immunodominant peptides recognized by TIL from two of these genes have also been identified. In two cases, the TIL that were used to identify these new genes were associated with significant in vivo antitumor regression. We thus believe we have cloned the genes that encode the melanoma antigens responsible for antitumor effects in humans. The cloning of these genes will enable us to insert them into vaccinia or other vectors for direct immunization against T cell recognized melanoma antigens. This represents a unique approach to the development of cancer vaccines.

Gene therapy protocols in the intramural program are also continuing. Twelve patients have now been treated with gene modified TIL utilizing the gene for tumor necrosis factor (TNF). We have seen one dramatic antitumor response with TNF gene modified TIL in a patient who had previously failed treatment with conventional TIL. This phase I escalation study has recently achieved (in the last patient) the full dose of IL-2 utilized in other trials. In clinical trials utilizing gene modified tumor, three patients have been treated with TNF gene modified autologous tumor and two patients with interleukin-2 (IL-2) gene modified tumor. Studies in these patients will continue.

Additionally, scientists at NCI and the National Institute of Neurological Diseases and Stroke (NINDS) are conducting a clinical trial using gene therapy to treat patients with primary and metastatic brain tumors. This therapy involves the administration of a murine retrovirus containing the herpes simplex thymidine kinase (HS-tk) gene. The tumor cells incorporate the HS-tk "suicide gene" allowing them to be killed by the administration of the anti-HS drug, ganciclovir. The interim Phase I trial results showed objective evidence of decreases in tumor size and/or consistency in over 60% of the patients treated. It is anticipated that the initial Phase I study will be completed shortly, and plans are underway to treat an additional 20 subjects with an improved vector producer cell line.

In September 1993, the NIH Recombinant DNA Advisory Committee (RAC) approved a pediatric protocol to use the same HS-tk gene and ganciclovir therapy at St. Jude Children's Research Hospital in Memphis. More recently, the RAC approved the same general strategy to treat patients with leptomeningeal carcinomatosis. NCI scientists have also developed a much clearer picture of the biochemical basis of the "bystander effect" which is so crucial to the anti-tumor effect of this strategy. Collaborations are ongoing with groups in Japan, Belgium, and France to further clarify this mechanism.

VACCINE DEVELOPMENT

Mr. Stokes. There are a number of new and exciting initiatives underway in vaccine development. Can you tell us about the research underway in this area that is examining the potential for patients to be immunized against their own tumor. This type of research offers tremendous hope for cancer treatment and prevention as well. How much is included in the FY 1995 budget request for this research initiative?

Dr. Broder. There are a number of innovative vaccine approaches to cancer treatment and prevention which are being pioneered at NCI. In great measure, these approaches have only recently become accessible because of new-found abilities to manipulate genes and genetic material in the laboratory and carry these new abilities to the treatment of cancer patients.

For example, one approach to vaccine development has been to modify the smallpox vaccine with additional genetic material. The smallpox vaccine has been one of the most successful vaccines in world health - its ability to provoke an immune response against the virus has led to the elimination of smallpox on earth. NCI scientists have now been able to modify to smallpox vaccine genetically to add genes which are specific to the cancer cell. The immune response to virus could then theoretically spill over to affect immunity against cancer. Already, a CEA-vaccinia vaccine is in trial for patients with colon cancer, rectal cancer, breast cancer and lung cancer. The early results of this study show that the vaccine is capable of causing an immune response, and further work is ongoing to determine the specificity of this response to tumor. A similar construct has been produced in which PSA is linked to vaccinia to produce a vaccine which may be useful in the treatment and prevention of prostate cancer.

A particularly novel genetic engineering approach to cancer vaccine development has just been used to treat the first patient in an NCI intramural clinical program. This vaccine takes advantage of the fact that certain genes, called suppressor cancer genes, are inactivated in the cancer cell. In this vaccine program, a biopsy of the patient's tumor undergoes genetic amplification in the laboratory to determine whether the suppressor gene is mutated in that individual patient's tumor. From this genetic sequence, it becomes possible to synthesize the protein predicted from the mutant genetic sequence artificially. This peptide can then be used in that individual patient as a specific immunotherapeutic vaccine. Work like this is only possible because of the ability to sequence genes from tiny bits of tumor tissue through the polymerase chain reaction, and to construct any peptide using protein synthesizers. This work is another example of how advances in molecular biology and its techniques and machinery can be translated to new approaches in cancer treatment and prevention.

Vaccines stimulate the host immune system so that its response to attack from outside the body (e.g. a virus or bacterium) or from within (e.g. a tumor) is strengthened, prolonged, or made more effective. Cancer vaccines could either prevent cancer development (a prophylactic vaccine), or augment the immune response in such a way that the disease is treated or recurrence is prevented (a therapeutic vaccine). NCI has been actively pursuing investigations into the development of cancer vaccines for some time. The current research strategy calls for two distinct areas of emphasis, based on our present comprehension of tumor pathogenesis and tumor biology. The first is prevention of cancer associated with viral infection by development of conventional vaccines against the causative virus. The second targets cancers of non-viral etiology, exploiting recent immunobiologic discoveries to develop vaccines directed against tumor-specific antigens.

For those cancers in which viruses play a major role, conventional prophylactic vaccines appear feasible. Such vaccines should be designed to prevent the initial virus infection, which would also prevent the later development of the cancers associated with that virus. Studies leading to the development of vaccines for virally-associated cancers have involved the human papillomaviruses (HPVs), which cause human cervical and anogenital cancers, the hepatitis C virus (HCV) which appears involved in causing human liver cancer, and the Epstein-Barr virus (EBV), which is etiologically linked to nasopharyngeal carcinoma as well as some Hodgkin's and non-Hodgkin's lymphomas. HPV studies focus on developing multiple vector systems to express HPV proteins in potential vaccines, and also on studies of strain variation in HPVs that are associated with human cancers. Other efforts involve the development of animal models for use in testing the safety and efficacy of potential papillomavirus vaccines prior to human trials. Vaccine studies of HCV include the identification of viral genes and their products, the identification of protective T-cell epitopes of HCV, and developing *in vitro* neutralization assays as intermediate end points for vaccine development. These studies offer a unique opportunity to explore the cellular immune responses to HCV-specific proteins and to define B- and T-cell epitopes which will be important in vaccine development. EBV research activities include protection studies against EBV lymphoma in a severe combined immunodeficient (SCID) mouse model, and also a phase I human clinical trial using an EBV peptide vaccine. The goal of the latter study is to induce EBV-specific cytotoxic T-lymphocytes (CTL), since such cells appear to play a major role in protection against EBV in healthy seropositive individuals, and they may destroy tumor cells bearing EBV proteins.

Research on vaccines for cancers of non-viral etiology, which are currently thought to be the majority of human cancers, have also made significant progress. Most of these cancers, whose etiology is unknown in many cases, would require a therapeutic vaccine approach, in which tumor antigens and/or modified cellular substances appearing during neoplastic processes are reintroduced into the patient to stimulate anti-tumor activity and prevent the spread or recurrence of the tumor. In some cases, emphasis has shifted from determining whether specific tumor antigens exist to actually defining the antigens, cloning the genes encoding them, and determining how they can be most efficiently used in vaccine development. However, the isolation of such purified antigens does not invalidate earlier vaccine studies which used whole tumor cells, but adds the possibility of additional approaches making earlier studies more fruitful or easier to interpret. Multiple phase I clinical trials have begun in women with CEA-positive breast cancer and in eligible patients with CEA-positive gastrointestinal and lung tumors using isolated tumor-associated antigens such as carcinoembryonic antigen (CEA), whose DNA has been inserted into the strongly immunogenic vaccinia vector.

Many common cancers (breast, lung, epithelial) are also associated with a mutated or truncated p53 gene and p53 protein, that in turn generate CTL. NCI investigators have recently developed the technology to isolate and rapidly synthesize tumor-specific immunogenic oncopeptides from the patient's own tumor cells. These oncopeptides can constitute an autologous peptide vaccine that selectively targets the tumor cells containing the mutant gene product. This would result in novel vaccines against an individual's own cancer. The finding that such human oncopeptide vaccines engender a specific CTL response in animal models forms the basis for a clinical trial being initiated in patients with diverse epithelial cancers commonly accompanied by p53 and/or ras mutations, such as breast, lung, or gastrointestinal cancers. Similar approaches may also apply to the BRCA-1 (breast cancer) gene.

Cancer vaccine activities are of the highest priority to the NCI. They are being supported throughout the Institute, and these coordinated and interdependent activities furnish an excellent example of how basic discoveries and techniques of virology and molecular biology can be beneficial in providing the materials and concepts needed for safe and efficacious vaccines against human cancers. The FY 1995 budget request includes $85.9 million for vaccine development.

AIDS VACCINE

Mr. Stokes. How much closer does this research bring us to having an AIDS vaccine, please elaborate.

Dr. Broder. Current research in cancer vaccine development to examine the potential for patients to be immunized against their own tumor may impact ongoing research on the development of an AIDS vaccine. Experimental cancer vaccines have been developed that are directed against specific and unique antigens expressed on tumor cells. These therapeutic vaccines are designed to stimulate the cellular arm of the human immune system to produce cytotoxic T-lymphocytes (CTL) specific to tumor antigens. The CTLs are expected to lyse and kill the tumor cells expressing the tumor antigen.

An important aspect of research on the development of AIDS vaccines focuses on evaluating HIV proteins for their ability to stimulate the cellular immune system to produce HIV-specific CTLs. Many scientists believe that cellular immunity is likely to be important in containing the spread of HIV infection in humans. Since HIV-infected cells express several HIV proteins, a CTL vaccine against these proteins may be effective in preventing the spread of virus to uninfected cells.

The injection of the simian immunodeficiency virus (SIV) was found to stimulate the production of CTLs in simian macaques that are specific to two major SIV capsid proteins. In laboratory assays, the SIV-specific CTLs lysed and killed cells expressing the SIV proteins, providing evidence for the potential usefulness of this technology in experimental viral vaccine development.

Thus, the current developments in immunizing patients against their own tumors may be useful in the preparation of AIDS vaccines. However, it will be necessary to isolate and identify specific proteins from AIDS virus-infected cells that can serve as a template for such vaccines. Potentially useful HIV epitopes recognized by CTLs have been identified and mapped. They have yet to be evaluated in humans.

SPORE

Mr. Stokes. I understand the Cancer Institute's SPORE program, initiated in 1992, is based on the concept of organizing a full complement of resources toward a specific cancer site such as breast cancer. Why does the institute consider this type of approach to be most effective? What are some of the other cancer sites that have been targeted for the concentrated and comprehensive approach.

Dr. Broder. The SPORE mechanism was developed to award grants which stimulate translational research in cancer sites of particular importance with respect to promoting the movement of basic research findings into patient and population research settings. It is basically still an experiment and we do not yet know how effective SPOREs will be.

Several years ago, the NCI perceived that basic scientists and clinical researchers were not working with each other in the most effective way possible to achieve translational research objectives. Our initial evaluation of the program last year indicated that basic and clinical collaborative research is being stimulated more effectively using the SPORE grant as a vehicle.

There are numerous other approaches being used by the NCI to achieve translational research objectives such as cancer centers, program project grants, cooperative groups, and developmental grants. The flexible design of SPOREs complements these other approaches.

At this time the main thrust of the SPORE Program will remain focused on breast, prostate, lung and gastrointestinal cancers. We are exploring ways in which SPOREs could be used to promote translational research in ovarian cancer, melanoma, and neurological tumors.

DIET AND CANCER IN AFRICAN AMERICANS

Mr. Stokes. I understand that there was tremendous response to the cancer institute's pre-application conference for this project, and that about 90 researchers participated in the workshop. What is the purpose of this type of workshop for potential research applicants? What were some of their primary concerns about the project, explain.

Dr. Broder. A national workshop to discuss Program Announcement PA-94-033, "Culturally Sensitive Intervention Strategies for Promoting or Implementing Compliance with NCI Dietary Guidelines among African Americans" was held on April 14th on the NIH campus. Topics related to grant writing were discussed as they specifically relate to this program announcement. The twofold purpose of the workshop was to provide potential applicants with more knowledge and insight into issues related to community nutrition interventions in African Americans and to increase potential applicants' knowledge and insight into the NIH grant process, including budget preparation, grants review, assurances and certifications.

The issues addressed at the workshop relate to community nutrition interventions in African Americans. These issues consist of an overview of the specific aims, background, and significance of dietary change among African Americans; various methodological issues related to research in this area, including research design and sampling, dietary assessment and cultural issues; and consultation with NCI staff for the discussion of potential research ideas.

The response to the Program Announcement has been tremendous.

Ninety-five potential applicants attended the workshop. Participants included both prominent scientists as well as less experienced researchers, representing various disciplines including, nutrition, and the social sciences. In addition, representatives from community-based organizations/agencies (i.e., community health workers) attended. In addition, approximately 200 to 300 transcripts of the workshop have been requested. Requests for the Program Announcement are estimated between 150 and 200.

The potential applicants had several primary concerns about the project. The first concern was the role and responsibilities of the NCI Program Director. It was explained that the role of an NIH Program Director is to monitor grant progress from a scientific perspective and to serve as liaison between the grantee and NIH. Second, the potential applicants inquired as to why there were no set-aside funds for this important area of research. It was explained to the participants that the NIH research grant pool would be utilized as the funding mechanism given other competing priorities of the National Cancer Institute.

Mr. Stokes. How much of the FY 1994 budget will be invested in this project? How much is built-in the FY 1995 budget for this project?

Dr. Broder. No set monies have been set aside for the funding of the dietary change for African Americans project. However, applications with scientific merit will be funded through the NIH investigator-initiated research grant pool of funds. We will also look very carefully to reach applications that may be close to but miss the payline. The actual funding level depends on the successful review and approval of applications submitted to the Division of Research Grants.

AFRICAN AMERICAN DIETARY CHANGE

Mr. Stokes. What is the track record of the study section that will review the applications for the African American Dietary Change program announcement [track record for approval of applications]?

Dr. Broder. The program announcement is an open invitation to investigators to submit research grant applications in areas of special interest to the NCI. The program announcement, "Culturally Sensitive Intervention Strategies for Promoting or Implementing Compliance with NCI Dietary Guidelines Among African Americans" (PA-94-033) was published in the NIH Guide on February 4, 1994. A workshop was held April 14 for potential applicants. The first applications are due June 1, 1994. The Referral Office of the Division of Research Grants makes the assignment to specific chartered or special study sections based on the scientific content of the application. Many of these applications are expected to be assigned to the Behavioral Medicine Study Section. Some may be assigned to other chartered study sections such as Epidemiology and Disease Control or Nutrition or to an ad hoc cancer study section. Since this is a new initiative, there is no review committee track record to report.

Mr. Stokes. When are awards expected to be made?

Dr. Broder. The first awards could be made in March 1995. Since program announcements are open solicitations, applications will be received, reviewed and considered for funding on a continuing basis in the future.

Mr. Stokes. What level of support are you expecting to provide for this project?

Dr. Broder. There is no specific set-aside of funds for a program announcement. The level of support will be determined by the relative competitiveness of the applications and the relative importance and impact of the specific research projects in the overall context of the National Cancer Program. However, we consider this an important area, and will look to fund good applications.

MINORITY RESEARCH INITIATIVES

Mr. Stokes. How does the Institute determine which minority research initiatives to fund? Are funds set aside to fund targeted minority research initiatives?

Dr. Broder. Special needs are identified in a variety of ways by the program staff of the NCI and developed into concepts that are presented first to the NCI Executive Committee for initial clearance and to the respective Boards of Scientific Counselors for discussion and approval. The concepts are further developed into Program Announcements or Requests for Applications (with designated set asides) that are announced in the NIH Guide for Grants and Contracts.

Yes, funds are set aside for minority research initiatives. In FY 94, four RFAs have been directed to minority populations. They are the Minority-based Clinical Oncology Program for $2.7 million, the Minority Enhancement Awards for $1.6 million, the Native American Women's Cancer Initiative for $1.5 million, and the Developmental Research in Native Pacific Population for $1.2 million.

MINORITY RESEARCH INITIATIVES

Mr. Stokes. How many minority research initiatives are currently funded by the Institute? Are funds set aside to support each of them? Explain.

Dr. Broder. NCI has developed a wide range of efforts designed to address the increased cancer burden borne by minority populations. These include a variety of networks, research, training and information projects that target minorities. NCI has also established collaborations with influential organizations, academia, the scientific community and the lay public to better reach underrepresented minority and medically underserved groups. Funding is set aside for many of these projects, with total NCI support for these efforts estimated to be $80 million in FY 1995.

NCI conducts epidemiologic, laboratory, and multidisciplinary studies in cancer etiology that are aimed at identifying and analyzing the high risks of cancer that prevail in minority and underserved populations. Investigations of unusual risks of cancer in minority populations are complemented with studies of cancer in their countries of origin. To this end, NCI is pursuing studies in Asia and Latin America. Other research is investigating the underlying mechanisms to account for biologic differences in cancer between Black and white populations in the U.S. to determine whether as yet unidentified racial factors contribute to the incidence and outcome of cancer. NCI also supports surveillance activities through its Surveillance, Epidemiology, and End Results (SEER) program that enable the identification of cancer rates, trends and patterns of occurrence according to racial and ethnic groups. These activities will receive an estimated $15.1 million in support for FY 1995.

The Institute is committed to increasing the participation of minority populations in NCI-supported prevention and treatment clinical trials. NCI's Minority-Based Community Clinical Oncology Programs, a network of community cancer specialists, primary care physicians, and other health care professionals, provide minority cancer patents with access to state-of-the-art cancer treatment and control technology. In addition, NCI supports a special initiative to increase minority enrollment in clinical trials conducted under the auspices of NCI's Clinical Cooperative Groups. Studies also encompass research that focuses on AIDS and its disproportionate effect on minority populations. NCI will devote $5.3 million to these studies in FY 1995.

NCI has established the National Black Leadership Initiative on Cancer (NBLIC) and the National Hispanic Leadership Initiative on Cancer (NHLIC). These community health outreach activities mobilize leaders in the business, scientific, medical, civic, religious, and lay communities in order to develop community coalitions to promote NCI's cancer prevention and control goals, identify barriers and risk factors, and stimulate community involvement. These activities are slated to receive $3.1 million in FY 1995.

Training initiatives are supported which seek to provide opportunities for young people at the high school and undergraduate level to gain hands-on laboratory experience and to foster an interest in biomedical research as well as provide opportunities for those who have pursued studies at the graduate level. The goal of these activities is to increase minority participation in biomedical research. The FY 1995 estimate for these activities is $13.3 million.

NCI actively promotes the prevention and control of tobacco-related cancers through cancer control smoking prevention and cessation activities that address the special needs of minority populations. These targeted efforts will receive $1.9 million in FY 1995.

NCI-supported Cancer Centers are committed to the support of community outreach education programs and engage in many activities for the prevention and control of cancer in special populations. Activities include public education and information, education for health care providers, and screening and detection services aimed at special populations, particularly disadvantaged groups who are at increased risk for cancer. An estimated total of $3.7 million will be expended in support of these efforts in FY 1995.

Outreach and education activities include prevention awareness programs directed at Black Americans, Hispanic Americans, and other minority groups. NCI's Cancer Information Service provides advice through a toll-free information number (1-800-4-CANCER) and conducts programs specifically aimed at the special populations most prevalent in the areas served by the 19 regional offices. NCI makes available Spanish translations of Cancerfax and Cancernet and has developed and distributed low literacy materials about cancer education that target specific populations. Other efforts address the need for community physicians and other health professionals to promote cancer prevention awareness among their patient populations. In FY 1995, the total for these activities is estimated to be $7.2 million.

NCI supports a wide range of cancer control interventions in special populations designed to reduce cancer risk in the following areas: smoking and drug prevention and cessation; nutrition education and diet modification; alcohol consumption and education; cervical cancer awareness through prevention and screening; sexually transmitted disease education; and breast cancer awareness through clinical examination and breast self examination techniques. Activities include the Dietary Modification Feasibility Study in Minority Women which explores the potential for dietary intervention, specifically fat reduction, to lower the risk of developing breast, colorectal, and possibly other cancers and cardiovascular diseases in postmenopausal women. Another initiative, Intervention Research among Hispanic populations, was undertaken in order to stimulate a wide range of intervention research activities designed to reduce cancer morbidity and mortality in these populations. The Avoidable Mortality from Cancer in Native Americans initiative seeks to identify key factors that contribute to avoidable mortality for specific cancers and to evaluate the effectiveness of community interventions. Quality of life studies, with an emphasis on psychosocial aspects in special populations, have been undertaken to provide culturally sensitive measures that will allow full participation of patients from diverse backgrounds in cancer clinical trials and will help to identify their specialized rehabilitation needs. A Request for Applications (RFA) was released to stimulate proposals in developmental research in Native Pacific populations with an emphasis on assessing their cancer prevention and control needs, identifying barriers and testing culturally appropriate intervention strategies. The Native American Women's Cancer Initiative was developed in response to the emerging needs of these women, with an emphasis on reducing cancer risk behaviors and improving their research skills in order to increase the number of Native American women in key research positions. The estimated level of support for these interventions in FY 1995 is $9.3 million.

Other studies in highly relevant areas of cancer research, while not specifically targeted to minority populations, are focused on cancers for which minority populations have been shown to be at disproportionate risk. These studies include relevant aspects of research in breast, cervical, ovarian, prostate, lung, colo-rectal cancers, as well as adult T-cell leukemia and multiple myeloma. NCI will devote $21.2 million for these studies in FY 1995.

In summary, NCI has broad-based efforts in all aspects of minority-targeted research and outreach initiatives and will continue to expand efforts in these areas.

EVALUATION OF NATIONAL CANCER PROGRAM

Mr. Stokes. Is the National Cancer Institute conducting an evaluation of the cancer program? If so, what are the results of that review thus far? How will the results of the review and evaluation be used to improve the cancer program?

Dr. Broder. In FY 1993, the NCI began a three-phase review of the National Cancer Program (NCP). The third and final phase of the evaluation of the NCP is now being conducted under the auspices of the National Cancer Advisory Board (NCAB).

In the first phase, six panels of experts identified advances in basic, clinical and applied cancer research and assessed the potential of this new knowledge to prevent cancer, reduce morbidity and mortality and improve survival and quality of life in cancer patients. Their findings were published in the *Measures of Progress Against Cancer* panel reports.

In the second phase, the testimony received during the last two or three years at meetings of the President's Cancer Panel about issues important to the review of the NCP and recommendations of the President's Cancer Panel Special Commission on Breast cancer were integrated into the evaluation.

In the third phase, the NCAB Subcommittee to Evaluate the National Cancer Program reviewed information generated in the first two phases and heard testimony from critics of the NCP and presentations on the role of government agencies and health care providers in the cancer mission, "chronic disaster areas," alternative medicine approaches to cancer treatment, and the concerns of cancer survivors.

Using this information, the Subcommittee has drafted a report that recommends the future directions of the NCP. This early draft is presently being reviewed by outside organizations and individuals, and their comments will be considered in preparation of the final report. The report includes advice on research, policy, administration, and resource priorities to advance the application and translation of research, and to maintain excellence and accelerate progress in basic research. The report of the Subcommittee will be presented to the Appropriation Committee in the fall of 1994. In consultation with the full NCAB, NCI will consider these recommendations in setting priorities for future cancer research directions.

LONG ISLAND STUDY PROJECT

Mr. Stokes. I understand that the NCI is supporting a comprehensive breast cancer project that is designed to cover the northeast region of the country, known as the long Island study project. What is the status of this project? What is the estimated total cost of the project?

Dr. Broder. NCI supports a broad and comprehensive program of breast cancer research in basic studies in cancer etiology, prevention, diagnosis, treatment and rehabilitation. In the field of cancer etiology NCI supports the complex and comprehensive Long Island Breast Cancer Study Project and the Northeast/Mid-Atlantic Study, with emphasis on environmental factors in breast cancer risk.

These two studies are addressing environmental factors and breast cancer in high-risk areas. Both studies are in collaboration with the National Institute of Environmental Health Sciences. Research in the Northeast/Mid-Atlantic study is well underway. The Long Island Breast Cancer Study has funded a small number of projects, is prepared to fund others and is still in the planning stage for major research grants.

Six studies in the Northeast/Mid-Atlantic Study have been funded at a total annual level of approximately $1.6 million per year. Research at Yale University School of Medicine will address organochlorine compounds and breast cancer risk. At Mount Sinai School of Medicine studies will look at environmental and genetic determinants of breast cancer. Studies of environmental risk factors and breast cancer will be added to the on-going Nurses'

Health Study at Brigham and Women's Hospital in Boston. Environmental and genetic issues in breast cancer will be studied at SUNY at Buffalo. Studies on electromagnetic fields, organochlorine compounds, and other environmental exposures in breast cancer will be conducted at SUNY at Stony Brook. The Johns Hopkins School of Hygiene and Public Health will look at environmental factors and breast cancer risk in Maryland.

COLLABORATION WITH NIEHS

The Long Island Study is part of the overall NIH research approach to the causes and prevention of breast cancer. NCI is working with the NIEHS staff and a group of selected experts on environmental breast cancer. A meeting was called to initiate cooperative studies and to begin the complex process of developing a set of protocols to address the measurement of environmental exposures, technology development and validation, and historical reconstruction of exposure in the Long Island population. Grantees will be collaborating with NCI and NIEHS intramural laboratory scientists and epidemiologists.

A case-control study of women with breast cancer, being conducted by SUNY at Stony Brook, in Nassau and Suffolk counties, was funded in September and is already underway as part of the Northeast/Mid-Atlantic Breast Cancer Study. This research has been extended as an important part of the Long Island Project. Other investigators are being peer reviewed. It is not yet possible to say specifically how many women will be included in this research, but NCI will certainly attempt to identify those who have developed breast cancer on Long Island within a window of time.

NCI is networking with federal, state, local agencies, and private companies. The are six NCI-designated cancer centers in the New York area that are a resource for the Long Island Project. They have joined to propose a cooperative research venture to be supported by NCI. All six centers have indicated strong interest in participation, including Cold Spring Harbor Laboratory on Long Island. The Laboratory is devoted to basic cancer research and is located on the border between Nassau and Suffolk counties, and has conducted a number of public forums on breast cancer and is expanding its breast cancer research program.

LONG ISLAND PROJECT STUDY DESIGN

The essential task is to answer the question as to why breast cancer rates are high on Long Island. A case-control study will be the key mechanism of the Long Island Study. NCI was directed by the Congress to look at a number of environmental exposures with an eye to breast cancer risk. New technology will be developed to measure and analyze certain exposures, including airplane emissions. These assays are not simple. Additional biological markers of individuals' cumulative exposure over years are needed, so creative approaches have to be developed. Exposures from contaminated water, soil and air will be considered. Exposures include the pesticide DDT and its metabolite DDE; the agents used in the nematode program, dichloropropane and dichloropropene; the termiticide chlordane;

hydrocarbons and metals in exhaust; solvents; PCBs and PBBs; various herbicides; and electromagnetic fields. The Long Island Study will map housing wiring, and measure household exposures to electromagnetic fields. As the detailed protocol is developed, attention will closely focus on those exposures that may be associated with estrogenic or antiestrogenic activity.

Highly technical new computer strategies for mapping geographic areas will be used to relate breast cancer cases, household residence patterns, and many environmental exposures such as contaminated water and other potential or suspected environmental hazards.

As planned, the Long Island Project includes a six-month first phase, a second phase lasting approximately two years, and a third phase of varying length for different objectives. The first phase is focusing on methodology development, recruitment of study participants, surveying area residents, developing collaborations and receiving input, and developing specific plans for a minority outreach program. The second phase will include continuing active participant recruitment, interviews, and specimen collection, laboratory analyses, and interim data analyses. The third phase will provide for continued recruitment and analysis of the various types of data collected plus the preparation of final reports.

INFORMATION DISSEMINATION

Because this research grew out of the concerns of Long Island women with breast cancer and their friends and families, an active program of contact with the citizens' groups has been maintained. Representatives of the NCI/Long Island Breast Cancer Project will join in networks of community groups and information will flow in both directions.

NCI has a valuable resource in its Cancer Information Service, the CIS, which offers information on cancer and cancer treatment via a toll-free 1-800-4-CANCER number. The nationwide service has regional offices and the Long Island area is covered by the CIS at Memorial Sloan-Kettering Cancer Center. Representatives of the CIS have been involved in all aspects of this research and the CIS Outreach program will be expanded to work with Project staff and the Nassau and Suffolk County Health Departments.

In addition to the amount set aside for the Northeast/Mid-Atlantic Study, NCI plans to spend an estimated $1.8 million in resources for research in 1994 for the Long Island Breast Cancer Study Project and over $4 million in 1995 President's Budget.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes. I understand that a number of the institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. Does the NCI make minority supplement awards, if not why not? And, if so, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Broder. Yes, NCI funds minority supplement awards. However, since the program is relatively new and many awards are made to individuals at an early stage in their training, relatively few investigators are at the point where they could be expected to hold their own independent research project grant award. There are at least two individuals identified as minority supplement awardees who have gone on to secure their own RPG awards.

HEALTHY PEOPLE 2000

Mr. Stokes. I understand that the Cancer Institute is the lead agency for the healthy people 2000 objectives for cancer and coordinates activities across the department of health and human services. What progress has been made with respect to reducing the risk of cancer in at-risk youth? What initiatives are underway and what initiatives are proposed for FY 1995?

Dr. Broder. It is estimated that 20 percent of all American children under 18 years of age live in poverty. These young people are extremely vulnerable to several unhealthy behaviors including: regular tobacco and/or alcohol use; sexual activity without the benefits of barrier protection; and unhealthful nutrition habits. These health-compromising behaviors put these children at high-risk.

The NCI has circulated a High Risk Youth Program Announcement. The two major research objectives of this program announcement are: to develop and test, through community-level institutions, methods and interventions for the primary prevention of cancers related to poor diet, tobacco use, alcohol use, and early or unprotected sexual activity; and to summarize and publish process and outcome results of these methods and interventions for use by community-level organizations that serve high-risk youth.

At this time, one application has received funding. The Program Announcement for High Risk Youth has been reissued recently to encourage applications over the next two years.

Smoking among youth has not been reduced significantly in the past decade. Although most smokers begin to smoke during early adolescence, few programs address smoking prevention until young people have already passed the likely age of onset.

The NCI plans to encourage the development and/or evaluation of smoking prevention messages and programs for delivery by pediatricians and other health professionals who interact with children under the age of 12 and of school-based smoking prevention programs for delivery in kindergarten through grade 3. In fact, 90 percent of tobacco users initiate use before age 21. As there are no well-evaluated tobacco use cessation programs aimed at adolescents, the NCI has plans to support research to develop and evaluate practical and easily disseminable adolescent cessation programs.

Smokeless tobacco use, a demonstrated cause of oral cancers, is especially prevalent among young males in the United States. Smokeless tobacco use is also quite prevalent in some sports.

NCI-supported research suggests that as many as 50 percent of minor league baseball players are regular users of smokeless tobacco. Preliminary activity has been undertaken with organized baseball to restrict and eventually ban the use of smokeless tobacco among players, many of whom serve as role models for American youth. Based on funding levels NCI would build upon the outreach activities developed thus far, such as the educational seminars for the Professional Baseball Athletic Trainers Society on the health effects of smokeless tobacco use and the involvement of Little League of America in discouraging smokeless tobacco use. In addition, the program would expand its position in organized baseball and include other relevant sports organizations in promoting the prevention and cessation of smokeless tobacco use, as well as evaluate the effects of this effort.

PROSTATE CANCER IN AFRICAN AMERICANS

Mr. Stokes. According to the American Cancer Society, African American males have the highest incidence of prostate cancer of any racial or ethnic group in the United States. About one out of nine African American males will contract prostate cancer compared with one out of eleven white males. How aggressive is the Cancer Institute pursing prostate cancer research? It appears that early detection is key to addressing this disease. To what extent are African American males participating in the Institute's prostate cancer clinical trial?

Dr. Broder. The National Cancer Institute (NCI) is studying and funding prostate cancer research at basic and clinical levels. There is controversy as to whether routine screening for prostate cancer in asymptomatic men is beneficial. In part, this is because of the highly variable behavior of prostate cancers and because of the morbidity which treatment can incur. Screening may therefore lead to unneeded treatment in some cases. Some of our work is aimed at distinguishing indolent prostate cancer, which is of little or no threat to the individual and which needs no treatment, from aggressive prostate cancer which might benefit from early detection and treatment. For example, research on determinants of prostate cancer biologic behavior is being done in the Prostate Specialized Programs of Research Excellence (SPOREs).

The Prostate, Lung, Colon, and Ovarian Cancer Screening Trial is designed to determine if routine screening for the four studied cancers saves lives. As part of the trial, 74,000 men will be randomly assigned to prostate cancer screening with digital rectal examination and measurement of serum prostate specific antigen (PSA) versus standard medical care. The trial opened in late 1993. To date 2,450 men have entered the study, about 2.5% of whom are African-American. NCI personnel are site visiting each screening center and working with them to refine established minority recruitment strategies which they provided in their original competitive bids for the contract to do the study. It may become necessary at the end of the pilot phase of the study to specifically compete for additional screening centers that can focus on minority recruitment.

AFRICAN AMERICAN EMPLOYMENT

Mr. Stokes. Within the Cancer Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In FY 1993, how many African Americans were at the GS-15 and above level?

Dr. Broder. There are currently four African Americans at the GS-15 and above level. One is in the Health Science Administrator series and two are in the Medical Officer Series. The fourth is in the Senior Executive Service (SES) and is a Deputy Division Director. One SES individual retired earlier this fiscal year. In FY 1993 there were four African Americans employed at the GS-15 and above level.

A new Acting Branch Chief has recently been appointed to serve as the Head of our Clinical Pharmacology Branch. This position is equivalent to a GS-15.

TAMOXIFEN STUDY

Mrs. Lowey. In light of the recent new data showing increased risk of death from uterine cancer and other serious side effects related to Tamoxifen, what is the department doing to reassess the ethical considerations of the tamoxifen prevention trial, where healthy women who have had no history of breast cancer (although they are at increased risk) are exposed for long periods of times to this potentially-dangerous drug?

Dr. Broder. From the inception of the Breast Cancer Prevention Trial (BCPT) all women considering entry into the study were informed of the increased risk of endometrial cancer associated with tamoxifen, as well as all other known side effects. The original risk:benefit calculations, as well as the informed consent document, were based upon an estimated increased risk of endometrial cancer of about two-fold. With the recent analysis of endometrial cancers observed in a large randomized placebo-controlled trial, risk estimates for endometrial cancer were changed to approximately a three fold increase. (This risk level is similar in magnitude to the risk reported for estrogen replacement therapy in postmenopausal women.) In addition, four deaths from endometrial cancer in that trial occurred in women who had been receiving tamoxifen. While the original consent document already mentioned potentially fatal complications of tamoxifen, the new information about the potential for death specifically from endometrial cancer was incorporated into a revised consent form which all women currently on the trial are being asked to sign as a condition for remaining on study. All women considering entry into the trial will also need to sign the revised consent form as a condition of study participation. In addition, all current participants on the study have been sent a letter detailing the new information about tamoxifen. Of note, the 10,600 women who have chosen to enter the trial to date are, on average, at considerably higher risk for breast cancer than the already elevated risk required for study eligibility.

The independent data safety and monitoring committee for the BCPT has met regularly since the start of the study. At each meeting, members review all new information about tamoxifen, whether from the BCPT or from other studies. They have also reviewed the risk:benefit assumptions for the trial on an ongoing basis, incorporating all new information. At the most recent meeting, on February 21, 1994, the committee recommended that the trial continue as currently designed. The committee is to reconvene on May 4 to again review all relevant information and make recommendations about study conduct and design. This committee has been notified of the reports of endometrial cancer associated with tamoxifen and of the rare deaths which have occurred. Since this is an investigational trial, the FDA also monitors all new information and can request changes in the study or consent document at any time.

COLON CANCER

Mrs. Lowey. You testified about the identification of a gene named MSH2, which is involved in many colon cancers as well as other cancers. Can you explain further the significance of this development and what it might mean for the prevention, diagnosis and treatment of colon cancer?

Dr. Broder. The MSH2 gene was the first of a series of genes shown to be associated with hereditary non-polyposis colon cancer (HNPCC), which accounts for about 15% of all cases of colon cancer. Mutations in MSH2 and related genes result in errors in repair of the cellular genetic material, DNA. DNA damage in normal cells results from errors during replication and from a variety of environmental insults. The inability to repair this damage can lead to loss of regulatory controls in the cell and ultimately to the development of tumors.

Since repair genes are present in all cells, mutations in these genes may also underlie the development of cancers in organs other than the colon. Cells normally contain two copies of each gene, but only one intact copy may be necessary for the cell to function normally. Members of HNPCC families appear to have an error in one copy of the gene in every cell. Subsequent mutations in the remaining copy can then trigger a series of events leading to tumor development. These additional mutations can be caused by errors during cell division or by environmental exposures. A possible explanation for the association with colon cancers relates to the fact that the colon is exposed to many potential carcinogens in foods and water, to the products of bacterial metabolism, etc.

Understanding and characterizing these genes can lead to development of tests to detect cells with critical mutations. This may help to identify individuals who are at increased risk for the development of cancer. These individuals can then be monitored more closely to detect cancers at an early stage when they are amenable to treatment and cure.

LONG ISLAND BREAST CANCER STUDY

Mrs. Lowey. I am pleased that the NCI is moving forward with the Long Island Breast Cancer Study Project, particularly in light of recent studies of the region which reinforce concerns about the elevated breast cancer risk for women living in the area.

What would you say to women who are worried about recent evidence pointing toward a heightened risk in the New York area?

Dr. Broder. Women in the New York area have reason to be concerned and should be vigilant in observing guidelines for screening and clinical observation for breast cancer. The reasons for high rates in this area are not well understood, but current evaluations on the relationship between various environmental and other risk factors and breast cancer are a prime concern of the NCI. The Long Island Breast Cancer Study Project has a complex and comprehensive approach for studying breast cancer etiology on Long Island. A case-control study and a matrix of other types of research should provide answers to this important question.

INFORMATION DISSEMINATION

Mrs. Lowey. Are you putting in place a mechanism to ensure that new insights gained from the Long Island Breast Cancer Study Project translate rapidly into clinical and community interventions that will make a difference to these women?

Dr. Broder. The Long Island Breast Cancer Project is designed to quickly translate insights gained from epidemiologic research to prevention strategies. As an NCI research effort, the Project will receive immediate benefit from all other NCI research insights and new developments. For example, a number of important genetic advances are thought to be imminent.

Plans are being made to gather the necessary biological specimens to allow for retrospective looks at genetic issues as appropriate. The unusually active link between research staff and community groups assures that information flows in both directions, keeping all informed of both problems and progress. Information or insights gained in this study will immediately benefit not only the women of Long Island, but women throughout the United States as well.

LINKING BREAST CANCER DATA BASES

Mrs. Lowey. The budget justification mentions that one of the goals of the Breast Cancer action plan is to expand the linkage of breast cancer databases and other information sources. What are the goals and timing of this planned expansion of data linkages? How will this improve our ability to respond to breast cancer?

Dr. Broder. Several activities are planned to expand linkage of breast cancer databases with other information resources that will improve our ability to respond to breast cancer. In response to the goal of the National Action Plan on Breast Cancer to "establish comprehensive patient data registries and materials banks as research tools," the NCI is convening a conference in September 1994 to assess currently available resources, the needs for additional resources, and the information that will need to be included in a national database to facilitate access to the resources. Linkage of registries and collections of patient materials, such as tumor tissue and blood or other fluids, can be expected to facilitate research efforts and overcome current barriers to progress in translating new laboratory findings into clinical application.

The NCI has already funded four institutions to establish a registry of breast cancer tissue with associated clinical and outcome data. These specimens and data will be made available to the research community through a peer review process and will facilitate research on diagnosis and prognosis of breast cancer.

Plans are already in place to expand the Breast Cancer Surveillance Research (BCSR) initiative. In order to more fully understand the effect of breast cancer screening on cancer outcome, data on screening practices and the biologic characteristics of tumors found on screening need to be collecte and linked to data from quality controlled population-based tumor registry programs. This research is not only important to determine the need for change in screening practices, but also to stimulate other breast cancer research.

Development of Geographic Information Systems (GIS) has permitted expansion of analytic epidemiology on the characteristics and determinants of breast cancer rates and risk. Ecologic analysis of databases created by population-based cancer registry data linked to Census files through geocoding are being conducted as part of cancer surveillance and etiologic research. The feasibility and utility of linkage of cancer registry information for other national health surveillance projects conducted by other federal agencies (e.g., EPA's National Human Exposure Assessment Survey and National Pesticide Survey, USDA's proposed activities under their 1989 Water Quality Program Plan, and CDCP's 1988 Agency for Toxic Substances and Disease Registries) will be considered during the next two years as the portfolio of environmental cancer studies increases. The relationship between breast cancer and environmental exposures, as well as the differential response of individuals exposed to carcinogens, can be explored through linkage of these data bases.

The NCI funded supplements to the National Health Interview Survey in 1987 and in 1992 to collect data pertaining to cancer control. Linkage of the 1987 data with the National Death Index has just been completed and the data are available for analysis of cancer risk factors. These data are available as public use files; publication of analyses from these data sources during the next two years is planned.

The NCI will continue to develop methods for linkage of data from population-based cancer registries to health claims databases. The NCI-HCFA linkage of the SEER cancer incidence data with Medicare data has provided an important resource for analytic research on cancer patterns of care and cost of care during stages of illness and recovery. Research is proposed for exploring the utility of other claims data bases for measuring the U.S. cancer burden and direct costs of care. These resources are being used for analyses of data on breast cancer patients by researchers at NCI and NIH, HCFA, and investigators affiliated with major cancer centers.

GENDER DIFFERENCES AND OCCUPATIONAL CAUSES OF CANCER

Mrs. Lowey. Can you update the Committee on the NCI's research into gender differences that make women more or less susceptible to particular cancer hazards in the workplace? If you had to rank the most serious occupational cancer hazards, for both men and women, which hazards would you include?

Dr. Broder. Recognizing the need to assess potential gender differences in cancer risks from occupational exposures, the NCI, along with the NIH Office of Research on Women's Health, the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health, sponsored a recent conference on "Women's Health: Occupation and Cancer." The conference brought together investigators from around the world to describe their work related to gender differences in cancer risk and to identify promising areas of future research. The conference proceedings will appear in the *Journal of Occupational Medicine* later this year.

NCI has a number of recently completed studies including ones in the field which will allow comparison of cancer risks from occupational exposures among men and women. The Case-Control Studies of Lymphatic and Hematopoietic Cancer in Nebraska was recently completed. This work focused on agricultural exposures, including pesticides. Women who are involved in treating livestock with pesticides have risks of non-Hodgkin's lymphoma and multiple myeloma that are higher than those observed among men. It is unclear, however, whether these higher risks represent differences in level of exposure, special susceptibility, or other factors, or simply occurred by chance.

In the mortality among aircraft maintenance workers study, a cohort mortality study of civilian workers at Hill Air Force Base in Utah, excesses of non-Hodgkin's lymphoma and multiple myeloma were associated with potential exposure to organic solvents. Relative risks tended to be higher among women than men, but the numbers were small.

In a study of cancer risks by occupation based on death certificates from 24 states, white men and women listed as farmers on death certificates had elevated risks of leukemia, non-Hodgkin's lymphoma and multiple myeloma. Male and female teachers tended to experience elevated mortality from multiple myeloma and non-Hodgkin's lymphoma. Soft tissue sarcoma was elevated among women employed in the telephone industry and breast cancer was associated with possible occupational contact with solvents and metals.

No strong differences in risk by job title or occupational exposure were noted between men and women in a study of occupational exposures and multiple myeloma among men and women in Denmark.

In a study of cancer mortality among furniture workers, an extended update of a cohort of the furniture workers found a nonsignificant excess of cancer of the buccal cavity and pharynx among black and white women, but not among men. Both men and women experienced small excesses of cancers of the stomach and pancreas.

A cohort study of approximately 40,000 women and 40,000 men exposed to benzene in China noted elevated risks for leukemia and non-Hodgkin's lymphoma in both sexes. Men, however, experienced an excess of lung cancer, whereas women did not.

A study of cancer mortality among jewelry workers showed that mortality from cancers of the esophagus, colon, and lymphatic and hematopoietic system was elevated among both men and women engaged in the manufacture of jewelry. Women experienced an excess of stomach cancer and multiple myeloma, while men did not.

The occupational mortality among women in a study of 15,000 cancer deaths among women in Russia noted many occupational associations previously observed among men, including stomach and lung cancers among miners, lung cancer among drivers, and leukemia among physicians and scientists.

In the mesothelioma and asbestos exposure study, occupational exposure to asbestos substantially increased the risk of mesothelioma among men and women.

There are also several ongoing investigations examining gender differences in occupational settings. The Agricultural Health Study is a long-term prospective study of men and women in Iowa and North Carolina and is designed to evaluate agricultural factors that may contribute to the development of cancer and other chronic diseases and reproductive outcomes. Information on agricultural exposures and lifestyle factors is being obtained from farmers and their spouses and commercial pesticide applicators. The cohort is expected to include over 30,000 women. Enrollment of cohort participants started in December, 1993 and will continue through 1996.

In a mortality study of dry cleaners, the follow-up of approximately 5,000 dry cleaners is being extended to include an not only those deaths prior to 1980 but an evaluation of the deaths from 1980 up to 1994. The cohort includes about 2,500 white women, 1,500 black women, 400 white men, and 900 black men employed in the dry cleaning industry who may have had exposure to dry cleaning solvents. An earlier evaluation of this cohort noted slight excesses of cancer of the bladder and lymphatic system, but with no substantial differences between men and women.

In the case-control studies of cancers of the brain and stomach, studies of these tumors are being conducted among men and women in Nebraska to evaluate agricultural exposures. Both cancers have been found to be elevated among farmers in many countries, but the specific factors that may be involved have not been identified.

The mortality experience of Hill Air Force Base employees is being extended from 1981 through 1994 to further evaluate the association observed in the earlier study between non-Hodgkin's lymphoma and multiple myeloma and organic solvents, particularly among women.

In the extended follow-up of formaldehyde workers the mortality experience of men and women exposed to formaldehyde is being extended from 1980 through 1994 to evaluate cancer risks that may be associated with exposure to this chemical.

Acrylonitrile, a major chemical used in the manufacture of plastics, is carcinogenic in animals. A mortality study of workers at eight facilities using or producing this chemical will be completed in 1996. This cohort includes about 5,500 women.

Well-established occupational hazards such as asbestos, chromium, benzene, arsenic, nickel, radon, benzidine, and wood and leather dusts will continue to exert their untoward health effects, even though recent control of exposures should diminish their impact in the future. Because of gender specific employment patterns in the past, men have had the predominant exposures to these substances.

Occupational exposures of concern today include pesticides, solvents, exotic metals, combustion products, and electromagnetic radiation. The evidence for the human carcinogenicity of these substances is not clear. However, these exposures are of concern to both women and men, because they can be found in occupational and non-occupational settings.

PROSTATE CANCER

Mrs. Lowey. The budget justification mentions two large-scale trials aimed at learning more about the treatment and screening of prostate cancer. Can you tell us more about the progress of these trials, including the timetable for their completion, and how they might impact the way we seek to prevent, detect and treat prostate cancer?

Dr. Broder. The Prostate Cancer Prevention Trial began enrolling men age 55 and over in mid-October. The trial is recruiting from 226 centers across the U.S. Interest in this trial, as measured by the number of men volunteering, has been very high. To date 11,800 men have volunteered to go onto the study and 3,750 men have completed the orientation period and have been randomized to receive finasteride or placebo. The trial will likely reach its accrual goal of 18,000 men in the first quarter of 1995. It will likely conclude in eight to ten years. It is hoped that the trial will demonstrate that several years of taking finasteride daily will decrease the risk of prostate cancer and benign prostatic hyperplasia (a non-cancerous swelling of the prostate). The trial will also provide information on the predictive value of screening tests in men taking finasteride.

The Prostate, Lung, Colon, and Ovarian Cancer Screening Trial began accruing men and women in late 1993. The trial has a number of objectives, one being to directly address the crucial question of whether routine screening of asymptomatic men for prostate cancer would save lives. The trial is enrolling 74,000 men and will last up to 15 years. An answer to the question of prostate cancer screening could be available before the conclusion of the entire trial, because trial duration depends on the number of endpoints for each cancer type and because prostate cancer is a very common cancer in men. The feasibility phase of the trial is due to last a year. To date, 2,450 men have entered the trial. The full scale trial is scheduled to begin in late 1994.

HISPANIC HIRING AND PROMOTIONS

Mr. Serrano. Dr. Broder, as you know, I raised questions with Dr. Varmus this morning regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. You are on the lucky first panel, but the others will not be neglected.

First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr Broder. NCI recognizes the need for targeted efforts to promote the recruitment of Hispanics in order to ensure their adequate representation in positions throughout the Institute. Working towards this goal, NCI has established a network with the Hispanic Association of Colleges and Universities and the Hispanic Centers of Excellence, both of which provide information for participating colleges and universities of current and future career and training opportunities available at the NCI. By making such information available, it is expected that there will be increased participation by Hispanic undergraduate and graduate students in furthering their research training as well as in seeking employment opportunities at the NCI.

Through the Summer Training Program, NCI is increasing the recruitment of Hispanics as well as other minorities, for high school, college, graduate and medical students and is making fellowship training programs available for Hispanics and other minorities who have received doctoral level degrees.

In addition to these efforts, NCI is also actively working to implement the new Federal Equal Opportunity Recruitment Plan (FEORP). NCI has developed a recruitment network encompassing 250 organization and institutions, 49 percent of which have indicated that they have a significant Hispanic population. As employment opportunities within the Institute become available, NCI will circulate these vacancy announcement to those minority institutions included in the NCI plan in order to increase the flow of applications from Hispanic applicants.

HISPANIC HEALTH ISSUES

Mr. Serrano. Second, what percentage of your Institute's budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Broder. NCI has established a number of research initiatives that specifically target Hispanic groups in order to meet the special needs of these populations. The projected funding levels for these projects in FY 1995 is estimated to be nearly $5.7 million. While this is less than one percent of the much larger total NCI budget of $1.9 billion, it should be noted that the majority of NCI funds are directed toward basic research efforts that will translate into measurable improvements in cancer prevention and treatment for all Americans.

Having said this, I would like to reiterate the critical importance that NCI places on minority-focused initiatives. To this end, NCI has developed a wide range of efforts designed to address the special needs of underserved minority groups, including those specifically directed toward Hispanic populations. These initiatives are as follows:

The National Hispanic Leadership Initiative on Cancer is a national outreach program that seeks to: (1) address the cancer prevention and control needs within Hispanic communities through the establishment of cancer prevention and control coalitions; (2) stimulate the involvement of Hispanic community leaders, both lay and professional, in Hispanic community cancer control coalitions; and (3) develop and support cancer control interventions and outreach activities in Hispanic communities throughout the United States and Puerto Rico. NCI has awarded two cooperative agreements to the University of Texas Health Sciences Center and the National Coalition of Hispanic Health and Human Services Organizations known as COSSMHO. Nine local project sites have been established across the country and in Puerto Rico by the University of Texas to address research questions and data collection relating to risk factors, epidemiology, and community-based cancer control activity. COSSMHO will focus on information dissemination and development of materials. Each grantee develops a network of co-investigators aiming to cover the 22.3 million U.S. Hispanics in order to design outreach activities specifically suited to the many groups within this diverse population. Baseline data collection and needs assessments are underway with the aim of advancing the Healthy People 2000 goals on cancer in Hispanic communities.

NCI supports intervention research in Hispanic populations, with the primary goal of stimulating a wide range of intervention research activities designed to reduce cancer morbidity and mortality. Hispanics do not currently experience excessive cancer rates to the same degree noted in other special populations. However, due to assimilation, it is anticipated that Hispanic Americans will, unfortunately, reach parity and may exceed cancer rates in the general population in the near future. Along with cancer surveillance, targeted intervention research becomes important for monitoring and addressing the cancer needs in this population.

Five breast and cervical cancer screening research projects have been funded which focus on preserving positive health behaviors associated with the Hispanic culture while simultaneously developing interventions to address their barriers to effective cancer control. A project entitled "Por La Vida Model in Cancer Prevention" at the University of California, San Diego is evaluating its preliminary findings. Focus groups of providers point out lack of knowledge of cancer, cancer risk factors, and cancer screening among Latinos. Concerns include the lack of health insurance and other enabling factors such as the complexity of clinical systems, long waits, insufficient time to provide education, and lack of options for referral. The women were concerned about cost of breast and cervical screening and strongly indicated a preference for female physicians.

The "Breast and Cervical Cancer Screening Among Hispanic Women" project at the University of Colorado, Boulder is evaluating methods for improving cancer screening compliance among Hispanics in six counties in Colorado. It features extensive collaboration between the state health department and various Hispanic organizations and health care providers to network effectively into the community. The project also includes a survey of physicians, nurses, and allied health care personnel to determine their health promotion and cancer prevention and control information dissemination practices and a survey of Hispanic males to determine their influence on the health seeking practices of their spouses.

The "Salud: Mexican-American Participation in the Prevention of Cancer" study at the University of Texas Health Science Center in Houston coordinates the efforts of multiple academic, state, and local institutions to deliver community-wide cancer control nutrition and screening interventions to two large Hispanic communities.

The "Cancer Control Among Hispanic Women" study at the University of California, Irvine is an ethnographic survey of 1200 women: 800 Hispanic and 400 Anglo. To explore for variations in cancer risk among Latinas, the investigators employed techniques that allow for sensitive communications and avoid previous assumptions about beliefs regarding cervical and breast cancer. Preliminary findings have been statistically analyzed and have convinced the investigators of striking differences in perceptions of risk factors for cervical and breast cancer among the groups studied.

This "Compañeros en La Salud: Cancer Control Among Hispanics" project at the Arizona State University, Tempe involves twelve pairs of churches in Phoenix and twelve pairs in San Diego to test the effectiveness of a cancer screening intervention and health promotion program. Reported preliminary data show that, although a significant difference in knowledge and understanding about cancer exists in the various churches, the baseline cancer screening data were surprisingly high.

Specialized information programs have been developed which are targeted to Hispanic populations. The Prevention Awareness Program seeks to increase awareness of and screening for specific cancers, notably breast and cervical cancers, through the development of specialized print and audiovisual educational materials needed to reach Hispanic audiences. Efforts to increase Hispanic participation in NCI-sponsored clinical trials involve expanded access to the Physician Data Query (PDQ) through Spanish translations of CancerNet and CancerFax.

NCI supports prevention and cessation trials that target tobacco use by Hispanics in an effort to develop culturally appropriate intervention methodology that can be used to successfully discourage smoking and other forms of tobacco use. Results from the Smoking Cessation Intervention in Hispanics based at the University of California in San Francisco will be incorporated into the large scale community demonstration COMMIT and ASSIST programs that seek to reduce tobacco use by some 90,000,000 Americans.

Special opportunities for understanding cancer etiology are presented by epidemiologic, laboratory, and multidisciplinary studies aimed at identifying and analyzing the high risks of cancer that prevail in minority groups. NCI has undertaken a pilot study to assess the feasibility of conducting large-scale epidemiologic studies of migrant and seasonal farmworkers. Special efforts are being made to include Hispanic farmworkers in the study population in order to evaluate the cancer experience of this underserved population. The project involves five interrelated objectives: 1) assess the accuracy of death certificate information on farmworkers; 2) determine the feasibility of tracing farmworkers over extended periods of time; 3) assess whether farmworkers are diagnosed and treated for cancer and entered into cancer registries or other relevant databases; 4) assess the ability to reconstruct lifetime exposure histories using interviews with farmworkers, their surrogates and employers; and 5) obtain quantitative environmental and biomonitoring exposure measurements on migrant and seasonal farmworkers.

Investigations of unusual risks of cancer in minority populations can often be supplemented by studies of cancer in their ancestral countries. For this reason, NCI supports studies of cervical cancer in Latin America in order to elucidate risk factors relevant to the high rates of this neoplasia among Hispanic Americans in this country. Likewise, in Puerto Rico, a case-control study has been initiated to investigate the role of tobacco and alcohol (including moonshine rum) and a variety of other suspected risk factors to determine why this area has such exceptionally high rates of oral and pharyngeal cancer.

One of NCI's highest priorities is to improve the nation's capability for measuring cancer rates and risks for specific segments of the U.S. population. NCI's Surveillance, Epidemiology and End Results (SEER) program has been expanded to include the nine million residents of the Los Angeles area, thereby increasing this national coverage to 25 percent of the U.S. Hispanic population. Collaboration with the Bureau of the Census is also improving the availability of regional population data to more accurately calculate cancer rates for special populations, including Hispanics.

In summary, NCI continues to support many research initiatives and outreach activities that are designed to meet the specialized needs of Hispanic populations. NCI pledges its strong and continued support for these efforts now and in the future.

HISPANICS IN BIOMEDICAL RESEARCH

Mr. Serrano. What programs does your Institute support to increase the participation of Hispanics in biomedical research including outreach to create a pre-university pipeline?

Dr. Broder. The National Hispanic Cancer Control Research Network (NHCCRN) is designed to increase the number of Hispanic investigators involved in cancer prevention and control studies. Thus far, NHCCRN has developed a "Quick Guide for the Preparation of Grant Applications" to assist investigators in competing for grant awards and is preparing a second publication, "Cancer Among Hispanics: A Profile," that will serve as an information resource to investigators conducting cancer research targeting the Hispanic population.

Significant Institute support to increase the Hispanic participation in biomedical research is also provided through the NCI's Comprehensive Minority Biomedical Program which includes several types of awards. Research Supplements for Underrepresented Minorities in Biomedical Research provide funds to minority individuals to participate in on-going research projects. This initiative is available to and utilized by pre-university minority students.

A second funding mechanism is the Cancer Centers Minority Enhancement Awards. These grants are awarded to cancer centers to extend outreach activities to minorities.

A third award is the Travel Award for Young Investigators, which supports participation of minority students at the annual meetings of the American Association for Cancer Research.

A fourth award is the Minority Health Professional Training Initiative, which supports clinical investigator awards for research in minority populations and faculty development awards in minority institutions.

Through co-funding arrangements with the National Institute General Medical Sciences, the NCI also supports minority research through the Minority Access to Research Careers and Minority Biomedical Research Support programs.

An outreach effort specifically designed to create a pre-university pipeline is the Science Enrichment Program (SEP), a residential science education/training opportunity to encourage youth from underrepresented minority populations to pursue professional careers in science research fields. During the summer of 1993 SEPs were conducted at four contracted sites for 169 incoming tenth-grade students, of which 18 percent were Hispanic American youths. The NCI anticipates an even higher percentage of Hispanic youth will participate in the 1994 program.

NCI also solicits students to participate in the NCI Student Research Training Program (SRTP), which hosts approximately 200 students per year and has over 60% minority participation. We are also in the process of establishing a Hispanic Adopt-A-School Program.

In addition, NCI is represented at seminars and workshops dealing with Minorities in Biomedical Research throughout the year. One major symposium attended was the Society for the

Advancement of Chicanos and Native Americans in the Sciences (SACNAS).

HISPANIC PARTICIPATION IN CLINICAL TRIALS

Mr. Serrano. What is your institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Broder. The Minority-Based Community Cancer Oncology Program (MBCCOP) is a network of community cancer specialists, primary care physicians and other health care professionals who conduct both clinical treatment research and cancer prevention and control research studies. This program was initiated to provide minority cancer patients with access to state-of-the-art cancer treatment and control technology. Since funding began in 1990, patient accrual from the MBCCOPs has grown to account for approximately 10 percent of all ethnic minorities enrolled in NCI-approved clinical trials. The MBCCOP RFAs were reissued in FY 1994 to continue the program, which funds eight programs with greater than 50 percent of new cancer patients from minority populations, including a new program in California which has a large Hispanic population. An expansion of MBCCOPS is planned in FY 1995 and will extend to new locations, physicians and patients/subjects. This expansion of the MBCCOPs is expected to significantly increase the accrual to clinical trials from minority populations.

The National Hispanic Leadership Initiative on Cancer (NHLIC) addresses cancer control barriers including risk factors, and cancer control service utilization in Hispanic communities as well as efforts to identify key factors that are associated with the low numbers of minorities that participate in clinical cancer trials. The NHLIC, through its membership, is encouraging the development of strategies to remedy these factors and ultimately increase the number of minorities who receive state-of-the-art prevention, diagnosis, and treatment interventions. The NHLIC has established nine outreach sites involved in mobilizing community leaders to promote awareness and utilization of culturally sensitive cancer prevention and control programs and to disseminate information on access to clinical trials through networking with national, state, local and community groups. The NHLIC plans to stimulate research on the development of strategies to increase participation of Hispanics in clinical trials and to motivate implementation of effective primary and secondary prevention efforts.

The NCI's Prevention Trials Decision Network (PTDN) is an integrated system for the coordination and prioritization of the Institute's large prevention trials. Such prioritization of large trials is particularly important in consideration of the large numbers of individuals who must be entered into such trials, the length of time before the full effects of a preventive intervention can be determined, and the large commitment of NCI resources required in such trials. One component of the PTDN is a committee with the primary responsibility of addressing minority recruitment and retention issues and the development of strategies to enhance accrual of minority populations to these large-scale prevention trials.

To improve access to clinical trials among medically underserved ethnic minority patients, NCI has initiated a program to increase accrual of such patients into clinical trials and to investigate the basis for observed differences in cancer incidence and treatment outcome among ethnic groups. It has been recognized that, in comparison with the general population, African American, Hispanic and Native American populations have a greater risk of developing cancer and are more likely to die from their malignancies. The reasons are poorly understood, but may be elucidated through the more active participation of minority groups in clinical trials. To extend the benefits of participation in clinical trials to minority populations, additional funding has been provided to the Clinical Trials Cooperative Groups by NCI to cover the costs associated with this initiative.

The Hispanic Cancer Control Program Initiative encompasses intervention research projects designed to address the high incidence of cervical and other controllable cancers in Hispanic women. These research projects also have an added emphasis to develop unique approaches for recruiting and retaining these women in intervention research. Intervention studies in progress include a survey of physicians, nurses, and allied health care personnel on cancer screening information provided to patients; a survey of Hispanic men's influence on the health seeking practices of their spouses; and the development of a number of culturally sensitive and linguistically appropriate materials and audio visuals. The NCI plans to develop a monograph on cancer among Hispanics based on the culmination of these studies.

Increasing minority recruitment to clinical trials as well as increasing overall recruitment to NCI-designated high priority clinical trials is a major priority of the Institute. The Patient Education Section (PES) of Office of Cancer Communication (OCC) continues to coordinate assessment and information initiatives for the lay and professional community. The general public is being educated via print, electronic media, interactive learning programs and educational videotapes which address participation in clinical trials. Health professionals receive updates on accrual through periodic mailings from the NCI, presentations by NCI staff at professional meetings and through publications in professional journals. The PES will work to enhance and expand existing mechanisms for informing patients, their families and the public about clinical trials. Distribution channels will be broadened to include special target audiences (African Americans, Native Americans, Hispanics and elderly Americans). Training programs and resources will be developed to educate physicians and other health professionals about how to counsel patients and families about the clinical trials process. Additionally, work with third-party payers will be accelerated to help provide them access to information they need regarding reimbursement decisions.

The importance of health-related quality of life in medical decision-making has evolved during the last decade. Patients and physicians are becoming more aware of the impact of cancer treatment on the quality of survival, compliance to treatment regimens, and participation in clinical trials. NCI's cancer clinical trials are including quality-of-life endpoints along with traditional tumor response, survival and toxicity outcomes. While many instruments have been developed for assessing health-related quality of life and specific quality-of-life domains in patients with cancer, few existing methods are appropriate for patients from diverse cultural backgrounds. To address the need for culturally sensitive assessment tools, NCI funded research in 1993 to develop/adapt, validate and pilot test techniques for measuring health-related quality of life in cancer patients from diverse cultural backgrounds. Instruments developed through this initiative will have immediate applications in cancer treatment, supportive care and psychosocial research among these cancer patients.

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Broder. According to data provided by the NIH Division of Research Grants, in FY 1993 the National Cancer Institute (NCI) had an overall success rate for Research Project Grants (excluding Small Business Innovative Research awards) of 22.0 percent. For those investigators identified as Hispanic, the success rate was 28.1 percent. The overall success rate for all identified minorities was 18.5 percent. For NIH as a whole, the success rate was 23.6 percent for RPGs for all applicants, 21.0 percent for Hispanics, and 19.6 percent for all minorities.

Hispanic investigators comprised 1.5 percent of the applicants submitting RPGs to the NCI in FY 1993. Members of minority groups made up 14.5 percent of NCI RPG applicants and 12.1 percent of the awards.

Program staff of the Institute make a concerted effort to encourage members of minority groups and women to apply for research grants and fellowships. We expect that our efforts in this regard will ultimately result in greater numbers of Hispanics and other minorities conducting research in the United States.

OVARIAN CANCER SCREENING

Ms. DeLauro. Is there any research underway into finding a screening test better than the CA 125 test?

Dr. Broder. As part of the Prostate, Lung, Colorectal, and Ovary (PLCO) study, transvaginal ultrasound (TVUS) is being tested in addition to CA 125 as a screening tool for ovarian cancer. Each of these two tests has potential advantages in the early detection of ovarian cancer. In contrast to the CA 125 blood test, TVUS is an anatomically oriented test to look for structural abnormalities in the ovaries rather than the production of a soluble molecule which is diluted in the bloodstream. It is, therefore, possible that the TVUS may prove superior to CA 125, or that the combined use of both tests is superior to either one alone in reducing ovarian cancer mortality. The PLCO is the first large scale definitive trial of TVUS and of CA 125 to see if either, combined with appropriate therapy, can reduce ovarian cancer mortality or morbidity.

Blood tests other than CA 125 are not yet tested sufficiently to put into a large scale trial. However, as part of the PLCO study, we are storing blood specimens on all 37,000 women who are screened. This will enable us to rapidly test future promising early detection blood tests as they become available. Potential candidates might be: serum inhibin, OVX1, and macrophage colony-stimulating factor (M-CSF). These tests are in the very early stages of development.

Ms. DeLauro. What is the "consensus approach" to prevention, detection and treatment of ovarian cancer that a panel agreed upon at the recent NIH conference?

Dr. Broder. The recent NIH Consensus Development Conference on Ovarian Cancer: Screening, Treatment, and Followup (April 5-7, 1994) was sponsored by the Office of Medical Applications of Research (OMAR) and the National Cancer Institute. The consensus approach for the conference was similar to that of previous OMAR consensus conferences. In brief, an independent, non-Federal consensus panel consisting of 15 members was convened to listen to presentations and discussion on the screening, treatment, and followup of ovarian cancer. The 15 panelists consisted of epidemiologists, gynecologists, nurses, medical oncologists, radiation therapists, and health consumers. The meeting was open to the public, patient consumers, press, and ovarian cancer and public health experts. Discussion periods were held during each section of the conference. On the third day, the panel presented a draft consensus statement based upon the information that had been discussed on the first two days of the meeting. There was an open comment period for recommendations from the audience, and final drafting of the consensus statement is in progress.

Ms. DeLauro. In the absence of a good screening test, do doctors generally have enough information and training as to what they should be looking for to try detect this cancer early -- getting adequate family histories, etc.

Dr. Broder. As part of every medical school curriculum, medical students are taught an appropriate medical history and physical examination, including family history and bimanual pelvic examination. They must be observed taking histories and doing physical examinations in order to pass their courses in physical diagnosis. In addition, practicing physicians are required to take continuing medical education credits that may involve state-of-the-art early detection technologies and procedures.

CANCER CAUSED BY AIDS VIRUS

Ms. DeLauro. I read with great interest the recent report that there is now evidence the HIV virus itself causes cancer, as opposed to just making persons with AIDS more susceptible to opportunistic cancers. How does this new understanding affect our ability to treat AIDS or other cancers caused by a virus?

Dr. Broder. A recently published article by Shiramizu et al. in Cancer Research described four cases of non-B cell lymphomas in HIV-infected patients in which there was evidence that HIV was integrated into the cell near a protooncogene. While more needs to be understood about these cancers, and the study needs to be confirmed in other laboratories, this NCI-funded report provides evidence to suggest that HIV directly caused the cancers in these patients.

It is already known that patients with HIV infection have increased susceptibility to a variety of tumors, including non-Hodgkin's lymphomas, Kaposi's sarcoma, anal carcinoma, and cervical cancer. Indeed, there is some evidence that as AIDS patients are living longer (as a result of antiretroviral therapy and better management of opportunistic infections) their overall incidence of non-Hodgkin's lymphomas is increasing. Also, there is epidemiologic evidence that the AIDS epidemic is causing an overall increase in the national incidence of lymphomas during the last decade. The available evidence suggests that HIV infection generally leads to the development of non-Hodgkin's lymphoma or Kaposi's sarcoma by several indirect mechanisms, including cytokine stimulation of the relevant cells and immunosuppression. Another retrovirus, human T cell leukemia virus type I (HTLV-I) can also cause leukemia/lymphomas, in part through its upregulation of cellular receptors for growth factors. The recent report by Shiramizu et al suggests that in rare cases, HIV may directly cause lymphomas in T cells or mixed cell populations by integrating near a protooncogene. This report serves as a reminder of the long-appreciated link between retroviruses and cancer and that retroviruses may lead to the development of tumors by a variety of mechanisms.

Because of the high incidence of lymphomas in HIV-infected patients, it will be important to better understand the pathogenesis of these lymphomas to develop preventive strategies. Better therapies are also needed. It should be noted, however, that the tumors described in the recent report are very rare (they are a small subset of AIDS lymphomas) and this finding should not have an overall impact on AIDS therapy. Also, while the finding will not have immediate impact on cancer therapy overall, it may lead to novel approaches to the treatment of these or potentially other oncogene-related tumors.

Ms. DeLauro. What are the implications of this finding on the possibility of developing an AIDS vaccine?

Dr. Broder. The results of this study could have broad implications for the development of an AIDS vaccine. It is not known at this time which, if any, of the HIV genes or proteins were expressed in these rare lymphomas. In all four cases analyzed, the HIV genome was integrated into the same human chromosome and very close to the same cellular oncogene. It is not known if the presence of the virus altered the expression of these cellular sequences.

Since the entire HIV genome from these tumors has not been sequenced, it is possible that these viruses may represent rare mutants that have an altered pathogenic or malignant potential. Alternatively, the presence of the virus may have altered the growth properties of a few preexisting cancer cells, providing those cells with distinct growth advantages. There is currently a World Health Organization proposal to assess the feasibility of developing a live attenuated HIV vaccine.

The observation of even a few cancers in the San Francisco cohort raises concerns on the advisability of conducting live-virus vaccinations using an attenuated non-pathogenic HIV-virus. As the AIDS epidemic moves into its second decade and HIV-infected people continue to live longer, more cases of these rare cancers may occur. Although the results implicating HIV in the etiology of rare T-cell tumors involved only a few patients who had the AIDS disease for nearly a decade, they do raise safety and ethical issues concerning the development of live-virus AIDS vaccines.

Ms. DeLauro. I understand this may also have negative ramifications on the use of retroviruses in gene therapy. Are any retroviruses currently being used in gene therapy?

Dr. Broder. There are no infectious retroviruses, per se, being used in gene therapy. Rather, portions of these retrovirus' genetic material are dissected to retain the capacity to transfer genetic material while deleting other portions of the genetic machinery necessary for viral replication. For example, in the clinical trial NCI successfully completed to transfer the ADA gene to children with severe combined immunodeficiency disease, the DNA message for the normal human enzyme replaced a portion of the viral genetic code which is necessary for the virus itself to reproduce.

All of the currently active gene therapy protocols use variations of this "designer gene" concept. It is likely that as we learn more about other retroviruses and their mechanisms of reproduction that new ways of carrying essential genes into human cells which lack them will be developed. This work will be important not only for replacing genes like ADA, but also for replacing tumor suppressor genes which become inactive in cancer.

Retroviral vectors designed for gene therapy are developed after first removing the viral genes that are harmful to the host, such as those that may be involved in the causation of cancer. Such vectors are unable to replicate in the host after initial penetration and, thus, cannot cause disease in the host. Their sole function is to act as the transporter of beneficial or normal genes to the host cell genome by inserting these genes into the chromosomes of the patient.

The process of inserting foreign genes into human chromosomes may lead to malignancies if the insertion occurs in such a way that it removes the normal controls over replication or alters other normal cellular functions. However, the possibility of cancers arising from these defective viruses is considered to be extremely remote, and most of the protocols involve patients with advanced cancers for whom the possible risks of other cancers are far outweighed by potential benefits to themselves or to other patients in the future. Currently, there are approximately 35 protocols approved by the NIH which involve the use of retroviral vectors in human gene therapy. Because of the very small possibility of harm to the host, investigators are now attempting to use other types of vector systems in gene therapy protocols, such as adenovirus or Herpes simplex vectors and non-viral vector systems such as liposomes.

Retroviruses are being used in human gene therapy in carefully controlled settings. The propensity of some retroviruses to cause cancer in animals and in humans has been known for years, before the recent preliminary finding that the HIV virus may be involved in the etiology of cancer in rare cases. Stringent safety precautions, including review of all protocols by the NIH Recombinant DNA Advisory Committee and the NIH Director, seek to assure that potential benefits to patients are weighed against possible risks. Finally, it should be emphasized that the possible involvement of HIV in cancer etiology is restricted to a rare subset of patients who have already been infected with HIV for many years.

Because of HIV's known role in the etiology of AIDS, it is unlikely that any proposals to use that virus as a vector in a population uninfected with HIV would receive serious consideration. Thus, it does not appear that the recent observation of a possible role for HIV in the etiology of some rare cancers has negative ramifications for the use of retroviruses in gene therapy.

BREAST CANCER

Ms. DeLauro. There was a recent announcement about a possible blood test to detect breast cancer. What is your feeling about this blood test -- does it appear to be promising to you?

Dr. Broder. Recently a new serum test to detect breast cancer was reported. The test was designed to detect a protein called p65. This protein is not specific for breast tissue. It has also been evaluated in the serum from men with prostate cancer. Many more studies will be required to determine the value of this test for either breast or prostate cancer. Since the protein is not specific to a given tissue, the test will not be useful for screening in asymptomatic individuals. The data reported to date are very preliminary, involving relatively small numbers of patients. Most of the reported data relate to the properties of the test and its ability to detect the protein rather than to the clinical utility. It could ultimately prove useful in monitoring the response to therapy and detecting recurrences early. However, there are no data to support these uses at this time. We need more research.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

VISION

Mr. Smith. How does your new planning document change the status quo for your Institute?

Dr. Olden. The planning document articulates the activities in which NIEHS needs to direct its future efforts in order to best fulfill its mission. This document will help university-based scientists as they develop new research applications. Internally it is helping us identify areas in which we need to reorganize in order to best meet these priorities. For example, the intramural program has been reorganized to allow experts in risk assessment to more closely work with toxicologists in designing assays that can address the need for a more mechanism-based toxicology and risk assessment methodology. The communication needs outlined in the document are leading to changes in our Office of Communication. Although the status quo will change, the direction of that change is consistent with the new opportunities and needs that the Institute's scientists have identified.

Mr. Smith. Has any funding been shifted among activities to implement the plan?

Dr. Olden. To date, the shifts in funding have been subtle, rather than dramatic. Extramural scientists have been solicited for their best ideas on studying environmental causes of breast cancer. Intramural scientists are pooling their resources to provide a more focussed effort in developing a mechanism-based data set for toxicology and risk assessment. The journal, *Environmental Health Perspectives*, has been given an expanded mandate and, using Institute staff representing a variety of different research interests, the journal has done an excellent job of providing a needed forum for communicating and discussing items of interest to the environmental health sciences community.

The planning document is providing a forum for discussing with the Institute's stakeholders the needs of future environmental health research. From these discussions, which are taking place this year, a firmer consensus on priority areas will emerge. Future directions and funding decisions at NIEHS will rely on these evolving priorities.

PRIORITIES FOR CHEMICAL TESTING

Mr. Smith. Last year you testified that you would be presenting recommendations to the Assistant Secretary for setting priorities among chemical agents for toxicity testing. What is your new policy, and how is that changing the waiting list of chemicals to be tested?

Dr. Olden. A new policy or philosophy is evolving for the selection of the best chemicals for study among the large number of chemicals in need of toxicologic characterization. Use of the new tools of molecular biology coupled with the experience we have gained in toxicology studies of literally hundreds of chemicals has allowed us to better understand the interactions of chemicals with biological systems. In some cases, we can predict the toxic or carcinogenic potential of certain chemicals or classes of chemicals with a high degree of accuracy. We believe that it would be in the best interest of public health if we focused our efforts and resources on those chemicals for which sufficient information is lacking to predict their biologic effects. We have discussed this new approach with the relevant regulatory and research agencies represented on the NTP

Executive Committee, and we will hold a workshop late this summer to examine the scientific basis for this new scheme and to identify the current statutory restraints on the regulatory agencies in the use of predicted outcomes for regulatory action. Increasing the role of predictive toxicology in our decisions regarding testing would not only allow us to focus further studies on the highest priority chemicals but also would dramatically increase the number of chemicals having a scientific basis for regulatory action.

MAMMALS/INVERTEBRATES/NON-ANIMAL MODELING

Mr. Smith. In the next decade, how much do you expect to decrease reliance on mammals in toxicity testing in favor of invertebrates or non-animal modeling?

Dr. Olden. The degree to which our reliance on mammals for toxicity testing will be decreased in the next decade will depend largely on the development and validation of non-mammalian and non-animal testing methods. The 1993 NIH Revitalization Act directed NIEHS to develop alternative methods that can reduce or eliminate the use of animals in acute or chronic safety testing. Significant opportunities exist to develop improved alternative test methods and models that incorporate recent advances in our understanding of the molecular mechanisms by which chemicals exert their toxic effects. Integrating these alternative non-mammalian and non-animal methods into testing strategies will facilitate more efficient animal use by identifying chemicals with the highest priority for evaluation. However, singly or in combination, these alternative assays cannot approximate the complexity of interactions that take place in a living animal. Thus, for the foreseeable future, non-mammalian and non-animal methods, such as invertebrates, fish, computer modelling and cell systems, generally will be used in conjunction with laboratory animal models. Where it is necessary to use animals, the Institute will continue to seek refinements to optimize animal well-being and to pursue strategies that will further reduce the number of animals required.

MEASUREMENT OF ENVIRONMENTAL HAZARDS

Mr. Smith. To what degree is your research hampered by the imprecision of measurement of environmental hazards, such as determining ground level exposure to airplane exhaust?

Dr. Olden. Estimations of the health effects of any pollutant are always dependent on the sensitivity and accuracy of measurements of exposure of persons to this effector. The current state of the art for analytical chemistry allows us to precisely measure pollutants and contaminants in any media, be it air, water, soil, food, and so forth at very low levels. Environmental health research, however, is hampered by the imprecision of the measurements of how much of the pollutants or contaminants are ingested and/or absorbed by an individual. Even if we have accurate measurements of what is out there in air, water, food, or whatever, we still have to know how much of this environmental contaminant was ingested and then reacted with sensitive tissues in the persons suffering that exposure. NIEHS is a leader in doing something about these many issues. One example comes from our Six Cities and Twenty-Four Cities studies at Harvard where for the first time accurate and sensitive measurements of children's exposure to several common air pollutants, such as ozone, nitrogen oxides, sulfur oxides, acid and fine particles, are being correlated with health effects. Another example of better measures of hazard is the devising of biomarkers of exposure. These biomarkers hopefully will measure not just what pollutant is out there but help quantify its biological actions on/reactions with sensitive tissues. One of our grantees is using such new biomarkers to quantify effects of polycyclic hydrocarbons in heavily exposed Eastern Europeans. The development of biomarkers of exposure is important to adequately perform epidemiology studies, to provide the dosimetry required to determine risk, and provide the required data needed by regulators to do accurate risk analysis.

The specific example of exposure to airplane exhaust is very difficult since it has been shown to vary so much with things like type of aircraft engine, frequency of takeoffs, distance from airport to exposed humans, aging of the exhaust, weather and so forth. Defining human exposures to and effects from such materials is very difficult and imprecise. Biomarkers of exposure would be most helpful here, but we have too few of these right now. While measures of what is in the air around airports is important for determining airport worker exposures, it is almost useless for estimating exposures to the general population for many more reasons than outlined above. The first step in assessing ground level exposures may be to develop modeling techniques to predict the dispersal and distribution of a standard airplane exhaust mixture to estimate what, if any, the risk of exposure to this mixture would be at ground level. After this analysis is complete, biomarkers of exposure could be identified to assess actual exposure.

CANCER MISSIONS

Mr. Smith. How can we distinguish between your mission and that of the Cancer Institute?

Dr. Olden. The most obvious difference between the missions of the NIEHS and the NCI is that NIEHS has the broader range of responsibility. Whereas NCI is dedicated to a single disease, cancer, NIEHS must consider a multiplicity of other possible health hazards, including birth defects, lung disease, neurological impairments, and immune disorders. Such a broad mandate dictates a multidisciplinary, multieffect mindset.

The NIEHS, because it can draw upon experience with how environmental agents can disrupt many biological functions, is naturally interested in understanding the environmental factors in cancer development. Also, the NIEHS has a prevention-oriented institutional mindset, as opposed to the more treatment and clinical-oriented mindset of Institutes devoted to studying a single disease or organ. The only area of potential overlap is in the arena of environmental causes of cancer.

Mr. Smith. Is it appropriate for NCI to look at environmental causes of cancer?

Dr. Olden. The health of the U.S. citizenry is best served by a combination of approaches and, for that reason, study of the environmental causes of cancer is appropriate for both the NIEHS and the NCI. Obviously, however, duplication of effort must be avoided. I think that NIEHS and NCI have a good track record of close collaboration to ensure that such duplication does not occur.

BUILDING ADDITION

Mr. Smith. What is the status of your new buildings at Research Triangle?

Dr. Olden. The NIEHS presently leases approximately 85,700 net square feet of laboratory and office space at several sites. To alleviate the logistical and financial burdens presented by this arrangement, the Institute developed a comprehensive plan to consolidate all activities, except material storage and distribution support, at one location. This plan, which has been partially funded, will add new space and renovate under-utilized existing space such as the high bay area. The new structures, when completed, will provide a 157,000 gross square feet laboratory module including an MRI facility, and a 57,000 gross square feet administrative module. Renovation of under-utilized existing space will provide 22 new research laboratories. Approximately $32 million has been appropriated to date for this project. Construction of the laboratory module is underway, boiler installation is underway, and renovation of the high bay area is nearing completion.

Mr. Smith. What is the total cost projected to be, and how much more funding is required to be appropriated?

Dr. Olden. The total cost of the project, assuming there is no major interruption to the time schedule, is estimated to be about $65 million. That would mean that an additional appropriation of $33 million is required.

Mr. Smith. In which years would this funding need to be provided?

Dr. Olden. In accordance with our current schedule, $10 million will be needed in fiscal year 1995 and $23 million will be needed in fiscal year 1996.

ASBESTOS STANDARDS

Mr. Smith. Last year we received quite a few letters criticizing your Institute for supporting a World Health Organization panel developing standards for asbestos. The letters contended that the panel was dominated by industry interests and that other U.S. agencies like NIOSH had declined to participate because of these concerns. How do you respond to these criticisms?

Dr. Olden. NIEHS has taken forceful actions to assure that WHO panels have proper balance and scientific expertise. I have met with WHO officials and proposed methods that have been adopted to improve the committee management practices of the WHO International Programme on Chemical Safety. I also had meetings on this subject with representatives of the other affected U. S. federal agencies and with the appropriate members of the DHHS and the State Department. My staff continues to monitor the IPCS program activities to assure that U.S. interests are met on asbestos and other environmental substances.

LONG ISLAND BREAST CANCER PROJECT

Mr. Smith. Tell us more about the nature of your involvement, both in terms of funding and staffing, in the Cancer Institute's Long Island breast cancer project.

Dr. Olden. We have been involved with the Long Island Breast Cancer Study Project (LIBCSP) since its inception. Presently, an NIEHS staff environmental epidemiologist is involved with the LIBCSP and is the project director at NIEHS. She works closely with NCI staff in all phases of the administration and provides advice on technical issues related to the measurement of environmental pollutants, methods available for the epidemiologic study of such pollutants, and related NIEHS-supported research.

The Long Island breast cancer project, as it is currently conceived, is divided into three phases: planning; implementation of research projects; and analysis and dissemination of results. It is currently in phase one, which is the planning phase. No funds have been expended by the NIEHS to support research activities on Long Island as of yet. However, this Institute provides $250,000 in support of six related cooperative agreements to study breast cancer in the northeast and mid-Atlantic regions and anticipates providing another $400,000 to support studies of environmental etiologies of breast cancer within the NCI centers program.

CHEMICAL TOXICITY AND CARCINOGENICITY STUDIES

Mr. Smith. In 1995, how many chemicals will be characterized for toxicity and how many will be tested for carcinogenicity in the National Toxicology Program?

Dr. Olden. New study starts estimated for 1995 include: 8-10 for carcinogenicity, 75 for genetic toxicology, and 50 for other endpoints. Testing studies could include one or more of the following study types: toxicity including special organ systems; carcinogenicity; chemical disposition; and genetic toxicology. In addition to the program of testing and methods development, mechanistic research is conducted in conjunction with testing.

CLINICAL PROGRAM

Mr. Smith. You are developing a clinical program. How large a role do you expect this component to play over time in your research portfolio compared to your traditional tasks of toxicity testing?

Dr. Olden. We are very enthusiastic about our clinical program. It gives us an opportunity to apply the knowledge that we obtain from experimental systems to address clinical issues. This approach will enhance our efforts to develop strategies aimed at addressing all aspects of the impact of environmental agents on human health including prevention, diagnosis and treatment. We have awarded two contracts for support of clinical research to Duke University and the University of North Carolina. The clinical program will be much smaller than our traditional programs in toxicity testing. We are designing the clinical effort to complement our toxicity testing efforts as part of our overall strategy to broaden knowledge on the toxicity of chemicals present in the environment. This represents our commitment to obtain information on a number of levels for chemicals that represent public health threats. These levels include the translation of basic knowledge in environmental health to the clinic and to regulatory officials. When we have experimental information coupled with clinical information, more informed judgments can be made on the potential for environmental chemicals to cause adverse health effects.

RESEARCH CENTERS ISSUE

Mr. Smith. Why are you planning to expand your use of Environmental Health Sciences Research Centers as a mechanism.

Dr. Olden. The Environmental Health Sciences Research Centers play an important role in addressing environmental issues throughout the country. They provide the Institute with necessary basic science for making decisions related to the prevention and intervention of environmentally-associated disorders. It is essential that the number of centers be increased and geographically distributed to meet the needs of affected populations through outreach and educational programs.

Mr. Smith. Will this include any expansion of the Marine Sciences Centers?

Dr. Olden. This would include an expansion of the Marine Sciences Centers so that they can continue the effective research on alternative models and utilize the models for innovative environmental health research.

Mr. Smith. Your justification describes a new mechanism -- developmental research centers. How many of these centers do you plan to award, and what will be the length of the grant?

Dr. Olden. The Institute plans to award two developmental centers per year if funds are available. The grants are a one time grant for three years so that the grantee can develop the capability to compete in our regular Environmental Health Sciences Centers Program.

Mr. Smith. Is the purpose of the centers to develop research on topics relevant to disadvantaged populations or is it to provide information and clinical services to these groups?

Dr. Olden. The purpose of these centers is to develop research on topics relevant to disadvantaged populations. In addition, the grantee must provide a plan for translating or linking the research activities to the patient care, educational, and other outreach activities of the center. However, no clinical services will be funded as a part of this initiative.

WORKER TRAINING RESPONSIBILITIES

Mr. Smith. How do you sort out responsibilities for worker training between yourselves, NIOSH, and the Environmental Protection Agency?

Dr. Olden. NIEHS and NIOSH have long, established programs of training in environmental and ocupational medicine, respectively, that are administered through competitive training grants to academic institutions and consortia. Responsibility for the special training of workers to enable them to work safely in the environmental restoration and cleanup efforts at EPA Superfund sites has been given to NIEHS by Congress. Funds are passed through EPA to NIEHS for this purpose and the training grants awarded by NIEHS have resulted in the required training of 400,000 workers. In fiscal year 1994, a similarly arranged program of worker safety training was initiated between the Department of Energy and NIEHS.

CHEMICALS AWAITING TESTING

Mr. Smith. How many potentially harmful chemicals have been identified for testing, but not yet tested?

Dr. Olden. There are a total of 25 chemicals that have been identified by the NTP Executive Committee and NTP Board of Scientific Counselors as having priority for long-term studies pending availability of funding. We are currently implementing a number of mechanisms to assure that the chemicals of greatest concern to human health receive the highest priority for study. Further, in its 1987 report to the Congress on "Identifying and Regulating Carcinogens", the Office of Technology Assessment referred to a National Research Council review of testing needs which estimated that only about 8% of 53,000 chemicals with significant human exposure had been tested adequately for carcinogenicity. That situation has changed little in recent years.

EPA/SUPERFUND FUNDING

Mr. Smith. Provide a five-year table of funds received from Superfund, broken down into research and worker training.

Dr. Olden. The following table provides a five-year history of funds received by NIEHS from EPA for carrying out our Superfund responsibilities:

YEAR	RESEARCH	WORKER TRAINING	TOTAL
1990	$16,000,000	$19,354,800	$36,254,800
1991	21,915,000	20,000,000	41,915,000
1992	30,640,000	20,500,000	51,140,000
1993	31.915,000	20,125,000	52,040,000
1994	32,914,800	20,000,000	52,914,800

AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY

Mr. Smith. Provide a five-year table of funding received from the Agency for Toxic Substances and Disease Registry.

Dr. Olden. NIEHS has a reimbursable agreement with the Agency for Toxic Substances and Disease Registry (ATSDR) to provide information to ATSDR on toxicological studies of chemicals and chemical mixtures. Costs incurred from 1989-1993 are as follows (Dollars in 000's): (1989) $4,926; (1990) $3,480; (1991) $1,155; (1992) $1,222; (1993) $317.

NTP FUNDING

Mr. Smith. Identify 1993-1995 funding for the National Toxicology Program from all agency sources.

Dr. Olden. The following table is inserted to display the past three years funding of NTP:

($'s in Millions)	NIEHS	NIOSH	NCTR
1993	$75.5	$5.1	$.4
1994	$76.6	$5.1	$.5
1995	$78.1	$5.1	$.6

RESEARCH CENTERS

Mr. Smith. Identify the number, type, and subject matter of research centers supported in 1994.

Dr. Olden. There are 15 Environmental Health Sciences Centers, including developmental centers, and 5 Marine and Freshwater Biomedical Sciences Centers presently being supported by NIEHS.

ENVIRONMENTAL JUSTICE

Mr. Stokes. Recently, President Clinton issued an Executive Order on Federal actions to address environmental justice in minority populations and low-income populations. Your Institute has taken a lead in this area. Elaborate on how your Institute plans to address environmental justice in its research, research training, and outreach initiatives.

Dr. Olden. One of this year's most important NIEHS accomplishments was a Symposium on Health Research and Needs to Ensure Environmental Justice that we held jointly in February with the NIH Office of Minority Health Research, the EPA, CDC, and DOE. This symposium brought together, for the first time, grass root advocacy groups as well as the biomedical research community. This forging of a common ground has tremendous implications both for improving communication and for developing a research agenda more responsive to real world experiences. Recommendations from this symposium will be used by a variety of federal organizations, including the NIEHS, to develop new research programs. Already the NIEHS has issued an RFA titled "Environmental Equity: Partnerships for Communications", which will fund projects that explore ways to link members of a community who are directly affected by adverse environmental conditions with researchers and health care providers. The NIEHS will continue its training programs aimed at encouraging representation from all U.S. groups.

Mr. Stokes. How much is included in the FY 1995 request for each of these initiatives?

Dr. Olden. The FY 1995 budget submitted by the Institute includes $9.1 million for environmental justice initiatives, $470 thousand for research training, and $500 thousand for outreach initiatives.

Mr. Stokes. In your professional judgement, is each of the amounts sufficient for the task at hand in each area?

Dr. Olden. The budget reflects appropriate amounts of funding for our programs under the current economic conditions. However, in my professional judgement, additional resources could be well used in each of the areas if there were no fiscal constraints.

AT-RISK POPULATIONS

Mr. Stokes. How is your Institute engaging at-risk populations in setting its research and outreach agenda?

Dr. Olden. In addition to the usual mechanisms,the Institute utilizes symposiums, such as its recent Symposium on Health Research and Needs to Ensure Environmental Justice, and upon its centers that are devoted to addressing the health needs of disadvantaged groups, to solicit the opinions of at-risk populations.

Mr. Stokes. Which budget and funding mechanisms are used to support this activity?

Dr. Olden. These efforts are funded through both extramural and intramural mechanisms.

Mr. Stokes. How much is included in the FY 1995 budget request for this effort?

Dr. Olden. These efforts account for approximately $2.5 million of the FY 1995 budget request.

LEAD POISONING

Mr. Stokes. The "Lead in Children" Clinical Trial. How is this clinical trial progressing?

Dr. Olden. The planning phase of this clinical trial, which is known as the Treatment of Lead-exposed Children, is almost complete, and the protocol is now at FDA. This is a multi-center, randomized, placebo controlled trial that is attempting to show whether oral chelation therapy, in addition to vitamin and mineral supplementation and home clean-up, is a safe and effective way of preventing lead-induced delays in cognitive development, altered behavior, and slowed growth. We plan to enroll about 1,300 (total) children from Columbus, Cincinnati, Philadelphia, Baltimore, and Newark, treat them when they are between 12 and 32 months old, and follow them for about three years. We hope to treat the first child in August, and enroll all the children by September, 1995.

Mr. Stokes. Are there "Lead Poisoning Prevention" programs underway in this area? Explain.

Dr. Olden. All of these cities have some kind of lead poisoning prevention program. The clinical facilities we are using for the trial usually serve a the medical referral site for children found to have elevated blood lead levels.

Mr. Stokes. In your professional judgment, what is needed most to address the lead poisoning problem?

Dr. Olden. Lead poisoning is an entirely preventable disease. People should not be exposed to leaded environments, but for millions, where they live is either unavoidable due to limited income or chosen occupation such as farming or specifically chosen location such as the "yuppies" moving back into a renovated inner city. However, lead safe housing for everyone is probably at least a generation away. In the meantime, we need to screen children, and we need to have sound, reliable data on safe, effective intervention methods for dealing with children whose lead levels are too high.

Mr. Stokes. Of these needs, which do you consider to be the most pressing unmet need?

Dr. Olden. We view the need to screen children, and to have sound, reliable data on safe, effective intervention methods for dealing with children whose lead levels are too high as the most pressing needs.

Mr. Stokes. What is the estimated cost of the research needs to address the most pressing unmet need?

Dr. Olden. The cost of the treatment of lead-exposed children clinical trial is expected to be approximately $29 million. We need new ways to approach the problem of exposure of the fetus to lead, because we know that damage occurs there. The requirements for safety of any intervention during pregnancy, however, are very stringent. At a more basic level, we need to know more about how lead affects the developing brain, when those effects are permanent and when they are reversible, and how we can reverse them.

ENVIRONMENTAL HAZARDS AND BREAST CANCER

Mr. Stokes. How much more do we now know about the effects of environmental hazards on the development of breast cancer than we did five years ago and how much closer are we to unraveling the relationship?

Dr. Olden. In the last five years we have become more confident about certain risk factors that are likely involved in breast cancer. However, other than genetic predisposition, which cannot account for the enormous numbers of women with breast cancer, consensus etiological risk factors have yet to be fully deciphered. Most scientists in this field would agree that we have now a reasonably good idea about possible risk factors of breast cancer, which include: genetic susceptibility/inheritance; early age of menarche; age of first full-term pregnancy; lactation; late menopause; dietary fat and diet per se; and environmental agents. Nearly 40 of the 450 agents we have so far studied for possible cancer in laboratory animals have been identified as causing cancer of the mammary glands. Including other research organizations that have done bioassays, about 75 of the 1000 agents studied adequately have been identified as causing cancer of the mammary glands in animals. We have reported these findings at the May 1994 meeting of the American Association for Cancer Research.

Those chemicals with convincing evidence of cancer in animals and that exhibit exposures to humans should be investigated as possibly implicated in the steady rise in incidence of breast cancer. Epidemiological studies will have to be done to confirm these findings in exposed populations.

Just recently several research reports have implicated certain chlorinated organo-halogenated-hydrocarbons, for example, pesticides, as being linked to increased risks of breast cancers. These chemicals include DDT, and certain metabolites, and lindane.

Long-term collaborative efforts at our Institute have allowed us to consider estrogens, endocrine-disrupters, and so-called xenoestrogens in the environment as representing potentially major sources of hormonal body burdens that may be associated with increased cancer risks. So we are making progress on a number of fronts. New developments into area of genetics occur almost daily and we are gaining a greater understanding of the mechanism by which environmental factors cause disease. It is in understanding this interaction between genes and the environment where we feel the answer lies.

GENE THERAPY

Mr. Stokes. What are the implications of gene therapy on research that is under the purview of your institute?

Dr. Olden. The Institute's initial efforts have been to apply our knowledge and experience in identifying environmental hazards to testing the "safety" of retroviral vectors that have been used in the NIH clinical gene therapy trials. Studies utilizing in vitro systems have been completed and no undesirable effects of the vectors were seen. Studies in animals are now underway. In addition, we are currently exploring the use of a transgenic mouse model for skin cancer for its possible use in studies of antisense gene therapy.

MINORITY RESEARCH INITIATIVES

Mr. Stokes. How does the Institute determine which minority research initiatives to fund?

Dr. Olden. I am committed to providing a real opportunity for minorities to participate in the NIEHS competitive research programs. In order to accomplish this I instructed NIEHS staff to develop new programs which are focused on the development of minority researchers and institutions. The hallmark for these programs is the staff involvement throughout the award period and a critical evaluation of the programs' success in meeting the objectives of each program. Particular attention is focused on the success of minority researchers in the regular NIEHS grant programs.

Mr. Stokes. Are funds set aside to fund targeted minority research initiatives?

Dr. Olden. I have reallocated funds from within the Other Research category, and the Training category to fund these new programs. In addition, I have instructed staff to provide advice to me on ways of increasing the success of minority researchers in the regular grant programs.

Mr. Stokes. How many minority research initiatives are currently funded by the Institute?

Dr. Olden. The NIEHS sponsors a number of minority initiatives. At present, the Institute participates in approximately ten initiatives related to minority research. Among these are the MBRS and MARC programs, the Minority Supplements program, and the Academic Research Enhancement Awards (AREA). In addition to these, the NIEHS has developed a number of its own minority initiatives including the Developmental Centers Grant program, the Minority Scientist at Minority Institutions program and the Environmental Equity: Partnerships for Communication program.

NIEHS also supports and participates in the Environmental Science and Management Fellows program, a collaborative effort between the National Urban Fellows program and Tufts University. This program supports the training of mid-career professionals who have significant managerial experience and culminates in a Master of Science Degree in environmental management.

Mr. Stokes. Are funds set aside to fund each of them? Explain.

Dr. Olden. I have allocated funds specifically to each of these initiatives based on the need and size of the effort. As I mentioned earlier, they are funded from both extramural and intramural resources.

MINORITY SUPPLEMENT ISSUE

Mr. Stokes. I understand that a number of the institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. Does the NIEHS make Minority Supplement Awards?

Dr. Olden. The NIEHS has awarded minority supplements since fiscal year 1989.

Mr. Stokes. How many minorities participating in the program have gone on to successfully compete for research projects grants?

Dr. Olden. None of these have yet to go on to successfully compete for research project grants. Of the four supplements awarded to minority investigators early in the program, three of these individuals completed their training in 1992 and one finished in 1993. Therefore, it is still too early in their careers for them to successfully compete for research project grants.

Mr. Stokes. Within the NIEHS, currently, how many African-Americans are at the GS-15 and above level and in what positions?

Dr. Olden. The Institute currently employs three African-Americans, one male and two females, at GS-15 and above. I am one, Dr. Marian Johnson-Thompson is head of the Office of Institutional Development within the Office of the Director, and Dr. Ethel Jacksonis Chief of the Scientific Review Branch in our Division of Extramural Research and Training.

Mr. Stokes. In FY 1994, how many African Americans were at the GS-15 and above level?

Dr. Olden. The same three personnel were employees in FY 1994.

SUPERFUND AND NIEHS

Ms. Lowey. As you know, the Superfund program has been the subject of much criticism in recent years. Evaluations have reported that more money is being spent on legal fees than on clean-ups. In addition to these issues, I am concerned about ensuring the scientific soundness of Superfund clean-up actions. Are you satisfied that EPA is making proper use of the information about environmental hazards generated by your Institute?

Dr. Olden. The effect of uncontrolled hazardous substances on human health is one of the most significant public health concerns facing the United States. The Congress recognized that the science base is inadequate and in the Superfund Amendments and Reauthorization Act (SARA) of 1986 established a university-based multidisciplinary basic research program at NIEHS known as the Superfund Hazardous Substances Basic Research Program. It is this kind of innovative approach that shows great promise for providing EPA with the answers to the problems of hazardous waste management and control. NIEHS has implemented a technology transfer strategy to disseminate nonproprietary programmatic and research information, providing a resource of contacts within the environmental sciences to link grantees with potential research collaborators in other governmental agencies, specifically EPA, universities, and industry. Further, we are also making every effort to work with EPA as they strive to make appropriate use of the data about environmental hazards as they become available.

RISK-ASSESSMENT

Ms. Lowey. The budget justification refers to the Institute's effort, in collaboration with the EPA and the Agency for Toxic Substances and Disease Registry, to establish a methodology for quantitative risk assessment. When will this methodology be complete and what are your plans for using it?

Dr. Olden. One of the major reasons for the large amount of uncertainty in current risk assessment practices is the lack of rational methods for establishing the shape of the exposure response curve in the low exposure region usually encountered in humans. Methods used to extrapolate high dose data in animals to estimates of risk for humans exposed to lower levels are usually not on a strong scientific foundation. The NIEHS, in collaboration with EPA and ATSDR, is developing methods to incorporate biological knowledge into the risk assessment process, especially in the area of improved prediction of dose response relationship. We have worked with EPA to develop a biologically-based model for estimating dioxin's effects in humans and are working with ATSDR on some of their priority chemicals.

EXTENDING RESEARCH FINDINGS INTO CLINICAL SETTINGS

Ms. Lowey. I was also interested in the Institute's efforts to increase the interaction between Institute researchers and clinical populations and facilities. I understand that the Institute has contracted for clinical research centers that provide this sort of access. What is your strategy for capitalizing on these links between basic research and these clinical settings?

Dr. Olden. The institution of a clinical research program is critical for NIEHS scientists to translate the basic science discoveries made at the Institute into the realm of human health. As with all the other Institutes conducting clinical research, this program will expand NIEHS's ability to study the health effects of environmental toxins, including prevention, diagnosis and treatment of environmentally related disorders in humans.

Ms. Lowey. Do you know where these research centers are going to be located?

Dr. Olden. NIEHS has awarded two contracts for support of clinical research to Duke University and the University of North Carolina. In addition to the clinical research studies, the contracts provide for support of a training program in which physicians and nurses spend one year in the clinical setting, learning how to do clinical research, and another year in the lab at NIEHS, learning the basic or applied laboratory aspects of environmental science. We have one physician trainee now, and are negotiating with three more. Recruitment of the nurses is underway.

Ms. Lowey. What are your goals for this effort?

Dr. Olden. We think that having researchers whose basic interests are in environmental sciences show a clinical presence, and in turn, exposing young physicians and nurses to environmental science will increase the familiarity of clinicians with environmental issues and also bring clinical problems to our laboratories. We hope our graduates will teach others in medical schools and schools of nursing; we hope that successful intramural clinical researchers will influence others to think of clinical applications and clinical experiments in their own areas.

HISPANICS AND NIH

Mr. Serrano. First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Olden. We are taking a proactive approach to increasing the hiring and promotion of Hispanics at the NIEHS. Ours was the first NIH Institute to employ and promote a Hispanic at the SES level. This research scientist also directed our first and only intramural clinical program. Regrettably for NIEHS, he has subsequently accepted a very attractive position with a leading pharmaceutical company. In leaving, he also took a technician-level Hispanic employee with him.

We have begun to identify potentially qualified minority applicants for recruitment and have established a mentoring program to assist present and potential NIEHS minority scientists to successfully negotiate the promotion and tenure system. One Hispanic scientist has been interviewed for a position and negotiations with this individual continue.

During the past twelve months we have employed two Hispanic Ph.D. scientists, one as a staff fellow and the other as a visiting scientist, and one Hispanic technician. Through the Stay-in-School Program, one Hispanic student is currently employed. The Stay-in-School mechanism holds promise in training students who may later become NIEHS employees.

On a larger scale, the "NIEHS/AACR Task Force on the Advancement of Minorities in Science" initiative has been undertaken to increase the pool of qualified minority biomedical scientists by developing initiatives starting at kindergarten and continuing through postdoctoral training.

Mr. Serrano. Second, what percentage of your Institute's budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Olden. Approximately 3.8% of our extramural budget is focused specifically on minority health issues. One of our extramural awards is to study the effects of environmental pesticides in birth defects in a Hispanic population in South Texas. Of our intramural and contract budget, approximately 7% targets minority issues. Examples of intramural minority health research projects include lead clinical studies and epidemiologic research on the prevalence of susceptibility genes in minority populations, analysis of mortality data for meat and poultry workers, and oncogene analysis.

Mr. Serrano. Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Olden. NIEHS is involved with several programs that address the issues of minority recruitment, participation, advancement, and retention in the biomedical sciences. With respect to Hispanics, NIEHS has actively recruited and involved Hispanic high school through graduate students in laboratory research through the Summers of Discovery program. Similarly, the annual Environmental Careers Symposium for high school teachers and students targets underrepresented minorities and, for the past two years, has included Hispanic representation. This Symposium introduces approximately 200 high school students and teachers each year to the wide variety of career options in the environmental health sciences.

One of NIEHS's most exciting involvements in pre-college environmental health science education is the Environmental Health Science Education R25 grant. This mechanism will fund the development of educational materials to infuse an environmental health science component into existing K-12 curricula on a national scale. While the awards will not be announced for two to three months, a number of the promising applications include strategies specifically targeting Hispanic students, including the development of bilingual materials. Current plans are to fund five or six of these projects for three years at a maximum funding level of $100,000 in direct costs per project per year.

NIEHS has recently embarked on the "NIEHS/AACR Task Force on the Advancement of Minorities in Science," jointly sponsored with the American Association for Cancer Research Minority Affairs Committee. The two-day Task Force meeting, held in early 1994, resulted in an action agenda to develop a comprehensive plan addressing minority issues at all levels of biomedical science education and training, beginning at kindergarten and progressing to support of pre-tenure Ph.D. scientists. Hispanic issues were prominent during the Task Force meeting and the subcommittee assigned the task of developing the comprehensive plan includes Hispanic representation.

NIEHS provides partial funding to support the Science and Math Investigative Learning Experiences (SMILE) Program through Oregon State University. This program is a partnership between Oregon State University and eight rural Oregon school districts to provide science and math enrichment for minority and disadvantaged students in grades 4-12. The purpose of the program is to increase the number of underrepresented minority students who graduate from high school qualified to go on to higher education and pursue careers in science, math, engineering, and the health professions. Most of the students in the SMILE Program are either Hispanic (39%) or Native American (37%).

The NIEHS has similarly provided partial funding for the "Inspirational Speakers in Science" Lecture Series through the North Carolina Health Careers Access Program, the "Elementary Summer Science Camp Program" through the North Carolina Science and Mathematics Alliance, and the "Expanding Your Horizons" Conference through the Research Triangle Science and Mathematics Partnership. Each of these programs target minority students, including Hispanics, to increase their interest and achievement in science and to expose them to careers in the life sciences.

The Regional Science Enrichment Programs, coordinated by the National Cancer Institute, provide hands-on science experience and mentoring for underserved youths. NIEHS has committed $100,000 for four years to support this project, which reaches out to Hispanic and other minority students through contracts to the University of Massachusetts at Amherst (16% Hispanic), the University of Kentucky, the University of Southern California at Los Angeles (46% Hispanic), and the American Indian Science and Engineering Society in Boulder, Colorado. Overall in 1993, 18% of the participants were Hispanic.

The "Symposium on Health Research and Needs to Ensure Environmental Justice," which had significant Hispanic representation, featured a breakout session led by NIEHS entitled, "Environmental Health Education in an Academic Setting: K-12 and Higher Education." Several Hispanic concerns were addressed during this session.

Within NIEHS a mentoring program is being established to assist young scientists in forming working relationships with more experienced scientist mentors. While open to all scientists within the Institute, a significant proportion of the participants are Hispanic.

NIEHS is also an active participant in the Stay-In-School Program, which allows students who are enrolled in a full-time course of study to work part-time in a scientific or administrative area within the Institute. Minorities, including Hispanics, currently account for more than 50 percent of the total participants.

Finally NIEHS, through the minority supplements to research grants program, currently supports eight Hispanic individuals at the undergraduate and pre-doctoral level.

Mr. Serrano. Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Olden. The NIEHS has only one external clinical trial program at this time. This initiative, the Institute's first, is a five-year clinical trial to determine the efficacy of succimer, a lead chelating agent, in reducing the elevated blood lead levels of children living in five inner city areas. In one of the participating centers, Newark, New Jersey, the population of children is 23% Hispanic. The clinical trial relies on referrals from health care providers to enroll children in the program. Retention is promoted through assurances that houses will be cleaned and children will receive vitamins and other medical care as well as incentives such as T-shirts, balloons, and hats. The portion of this project dealing directly with Hispanics will cost approximately $2 million over five years.

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Olden. The NIEHS received 475 applications last year and awarded 100 competing grants. Fourteen of the applications were submitted by Hispanics, and there was a 16% success rate, compared to the overall applicant success rate of 21%.

DISEASE RESEARCH

Ms. Delauro. How much will your Institute spend on disease prevention research in FY 1995?

Dr. Olden. We estimate that in FY 1995, NIEHS will spend about $219 million on prevention research. This research includes basic biomedical research aimed at discovering the environmental components of disease, applied toxicological research, and clinical research investigating treatments for environmentally related diseases and disorders.

Ms. Delauro. How does this compare to FY 1994, and FY 1993?

Dr. Olden. The FY 1994 and FY 1993 figures for prevention research are $217 million and $206 million respectively.

Ms. Delauro. How much will your Institute spend on occupational disease research in FY 1995?

Dr. Olden. NIEHS has and will continue to have a strong program in studying occupational exposures and diseases as part of our mission to investigate the environmental causes of disease. In FY 1995 the Institute will fund approximately $9.6 million of research in this area. Ongoing research includes epidemiologic studies of reproductive function in semiconductor workers exposed to a variety of solvents and metals, the pulmonary effects of exposure to grain dusts in farmworkers, and a study investigating the effects of exposure to mercury and nitrous oxide in dental hygienists.

Ms. Delauro. How does this compare to FY 1994, and FY 1993?

Dr. Olden. In FY 1994 and FY 1993, the Institute allocated $9.4 million and $9.2 million respectively to occupational disease research.

COMMUNICATING INFORMATION

Ms. Delauro. Do you have a program whereby you can quickly transmit new information about occupational hazards to businesses?

Dr. Olden. NIEHS has several methods in which businesses can obtain information about occupational hazards. The National Toxicology Program (NTP) publishes in the Federal Register announcements of meetings during which the results of studies will be discussed. These meetings are open to the public. Also NTP test results are published and are available to any interested party simply by calling the Institute.

The Institute also publishes the Biennial Report on Carcinogens. This report contains all known carcinogens and other compounds that are reasonably anticipated to cause cancer. Much of the research that determines whether a compound is sited is carried out under the NTP. NIEHS works closely with other agencies within the NTP such as the National Institute of Occupational Safety and Health that are directly charged with interacting with businesses.

Another program managed by NIEHS is the Superfund Hazardous Waste Worker Safety Training Program. This program, which is funded through an interagency agreement with the Environmental Protection Agency, provides hands-on training in the safe containment, clean-up, and remediation of hazardous waste spills and Superfund sites. To date, over 500 thousand individuals have received training sponsored by this program.

The Institute is currently planning a new activity in communications. A toll-free hotline to provide information on all aspects of environmental health is in the planning stages at this time. Once the hotline is established, we will make public announcements advertising the service in trade journals, newspapers, and the scientific literature.

NATIONAL INSTITUTE OF DENTAL RESEARCH

NEW AMALGAMS FOR DENTAL FILLINGS

Mr. Smith: In previous years you have testified about the need to develop new amalgams for dental fillings, and the Committee has encouraged this effort. Your budget justification describes a Cooperative Research and Development Agreement (CRADA) that has produced a new amalgam. Does this CRADA culminate the research effort or does more work remain?

Dr. Löe: This CRADA marks the initial steps in the development of new, non-mercury-containing amalgams for dental fillings. A prototype material has been developed, and additional refinements, as well as testing for serviceability, acceptability, and biocompatibility, remain to be completed. The NIDR research effort on this initiative is expected to continue for several years.

HARD TISSUES DISORDERS CLINIC

Mr. Smith: You have proposed that a hard tissues disorders clinic be established at the NIH Clinical Center. Although NIH has not previously had the capacity to study cartilage and bone conditions, is this something that is broadly researched in the extramural community? Why does NIH need to develop a capacity in this area?

Dr. Löe: Although selected problems or areas are under investigation in the extramural community, no single institution has the organizational strength and capability--as does NIH--to bring to bear the full and combined forces of basic science and clinical investigation. A multidisciplinary approach is particularly critical for the comprehensive study of hard tissue disorders (such as osteoporosis, osteoarthritis, and Paget's disease), which encompass such diverse fields as protein and mineral chemistry, cell and molecular biology, endocrinology, and biomechanics. The close relationship that exists between basic scientists and clinicians at NIH is essential if we are to rapidly translate advances in the basic sciences into tangible health benefits.

It is important to note that we are not competing with the extramural community; we are adding another dimension to their individual efforts and thereby increasing the likelihood that real health benefits will accrue sooner in this area.

RESEARCH CENTERS

Mr. Smith: You are projecting a change in the mix and number of research centers in FY 1995. Tell us more about which types of centers you plan to fund.

Dr. Löe: The number of NIDR-supported centers will decrease from 28 to 27 in FY 1995. This reflects the funding of three full-scale rather than the current six developmental Regional Research Centers for Minority Oral Health, and minor adjustments among the specialized centers in such areas as caries, materials, and craniofacial anomalies, which have been recompeted and are currently being reviewed.

Mr. Smith: How strong a research focus do you expect your minority research centers to have? Does their mission include an emphasis on community outreach?

Dr. Löe: The Regional Research Centers for Minority Oral Health were designed to conduct biomedical and behavioral research on particular oral health problems faced by different minority groups. The current developmental centers already are conducting numerous research projects and are establishing functional collaborative arrangements to focus the unique intellectual and material resources of minority institutions with those of research-intensive institutions on specific diseases and conditions. Outreach programs to clinics, community hospitals, and undergraduate colleges serving minority populations already are in place. The full-scale centers to be awarded in FY 1995 should reflect these types of components and permit expanded basic and clinical research activities on oral diseases and conditions that disproportionately affect minority populations.

SURVEY OF ORAL HEALTH STATUS IN SCHOOLCHILDREN

Mr. Smith: You support a survey of schoolchildren's dental status. Is this information covered in the NHANES survey conducted by the Centers for Disease Control?

Dr. Löe: The NIDR surveys of schoolchildren have included examinations of approximately 40,000 children in grades kindergarten through high school. This sample size is necessary to detect the oral disease changes that occurred in this population. The National Center for Health Statistics (NCHS) provides national estimates of selected oral diseases at approximately 10-year intervals for the U.S. population, and includes relatively small samples of school-age children. An NIDR evaluation of the statistical design of the 1988-1994 NHANES survey has shown that the sample size yield for school-age children will not be adequate to address the detailed substantive oral health information needs of the Department (e.g., progress toward the Year 2000 oral health objectives) or of the NIDR need to track oral disease trends in children. This inadequacy stems partly from the age categories that were used in the design of the NHANES III sample. Preliminary analyses of NHANES III oral health data (in progress) are also revealing that, despite the oversampling of African Americans and Hispanics in this survey, the available sample sizes are still too small for detailed analyses. Consequently, a new, independent survey of school-age children will be necessary to assess changes in oral health status not only in the general population but also in high-risk groups.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject matter of research centers supported in FY 1994.

Dr. Löe: The NIDR expects to fund 28 research centers in FY 1994, including five non-categorical Research Centers in Oral Biology; two Oral Health in Aging Centers; three Periodontal Diseases Research Centers; two Caries Research Centers; one Pain Research Center; three Craniofacial Anomalies Research Centers; three Materials Science Research Centers; three Clinical Dental Research Core Centers; and six planning grants for Regional Research Centers for Minority Oral Health.

ORAL HEALTH INFORMATION CLEARINGHOUSE

Mr. Smith: How many requests has your National Oral Health Information Clearinghouse received since its inception in January?

Dr. Löe: The National Oral Health Information Clearinghouse, a resource for special care patients and health professionals, has received 545 inquiries by mail, telephone, and electronic mail between January 1 (the date the service became available to the public) and April 22, 1994.

COST SAVINGS FROM DENTAL RESEARCH

Mr. Porter: I understand that NIDR's approximate 3 billion dollar investment from 1950 - 1990 in applied research resulted in the development and adoption of preventative approaches including fluorides, dental sealants and appropriate diet and hygiene, and has resulted in annual estimated potential savings of between 3 and 4 billion dollars in reduced treatment costs. Would you please elaborate on this point, and share your expectations for similar cost saving advances in the next 10 years?

Dr. Löe: The cost savings in dental expenditures resulting from the adoption of research-based preventive approaches are actually estimated at $5 billion annually and are projected to accelerate as increasing numbers of individuals experience less oral disease than preceding generations. Research targeted at identifying risk factors for high-risk populations as well as continued efforts to transfer scientific knowledge on disease prevention should provide additional savings from the ravages of common oral health problems. Rapid advances resulting from molecular biology and genetic epidemiology research should enhance our capacity to manage periodontal diseases, soft tissue lesions, functional problems such as temporomandibular disorders, pathophysiological problems of salivary glands, and severe genetic deformities. Such advances have great potential for substantial additional costs savings as well as reduced human suffering.

COST OF CHRONIC PAIN CONDITIONS

Mr. Porter: Your budget justification mentions that an interagency task force will develop the final report on the incidence and health care costs associated with chronic pain conditions. Can you tell me what the findings of the task force were and when we can expect the report to be released?

Dr. Löe: The NIH Revitalization Act of 1993 asked that NIDR take the lead in the development of a report, due in June 1995, of the incidence and direct health care costs associated with seven chronic pain conditions: low back pain, temporomandibular disorders, reflex sympathetic dystrophy, diabetic neuropathy, post-stroke pain, phantom pain, and post-herpetic neuropathy. An NIDR internal working group was formed, and a two-phase proposal was developed involving the preparation of state-of-the-science papers by experts. The proposal was submitted to relevant NIH Institutes, the Office of Research on Women's Health, and the Agency for Health Care Policy and Research. Representatives from these organizations constitute an Interagency Task Force on Chronic Pain, which has met several times to review and refine the proposal and suggest names of authors who could address the epidemiological and cost issues. We are now in the process of arranging for the preparation of these papers, which will form the framework of the report. The Interagency Task Force will supervise the production of the final report and recommendations.

SIGNIFICANT ACHIEVEMENTS

Mr. Porter: Dr. Löe, in the course of your tenure as Director of the National Institute of Dental Research, what would you say were the most significant achievements; how did oral health research most conspicuously move ahead under your watch?

Dr. Löe: The mission of the NIDR, as stated at the time of its establishment in 1948, and as it has been for the entire 46 years of its existence, is to improve the oral health of the American people. We decided in the early 1980s that it was important to assess how well we were doing, and that a broad-based program in oral epidemiology should therefore be established. National surveys conducted by this program during 1985-1987 showed that 50 percent of the 40 million schoolchildren of America had never had a cavity in their permanent teeth, and that substantial improvement had occurred in the adult population as well.

From these and other data, it was estimated that the total annual dental expenditures--adjusted for inflation--grew very slowly during the decade of the 1980s, even in light of the fact that more and more Americans were seeking dental care.

It was also documented that the ability of dentistry to hold the line on health care costs was directly related to advances in oral health research. Economists estimated that the declines in toothlessness and in the prevalence and severity of oral disease translated into savings of approximately $5 billion in the nation's dental bill in 1989. This is a saving in one year of over twice the total appropriation for the NIDR from its inception in 1948 through the current year, 1994.

I do not want to mislead you into thinking that the nation's oral health problems have disappeared. Every one of us remains at risk for oral diseases, and for millions of Americans these are severe problems. While it is heartening to note that half the children have no cavities, this also means that 50 percent still do. We also know that African Americans and Hispanics have worse oral health than nonminorities. Our oldest citizens have the worst oral health of all, with over 40 percent having lost all their teeth, while those who still have teeth continue to get cavities and suffer the most severe and extensive periodontal diseases of any age group.

Besides providing an inventory and serving as a basis for cost estimates and assessments of the demand for dental professionals and auxiliary personnel, the data analysis also fostered a planning effort and an evolution of the oral health sciences from a narrow concern with teeth and gums to encompass all oral and craniofacial tissues in health and disease. This evolution was outlined in two long-range research plans entitled Challenges for the Eighties in 1983 and Broadening the Scope in 1990.

Because the mouth mirrors the overall health of an individual, our mission includes research on systemic diseases that affect the oral and craniofacial tissues, as well as on the effects of oral disease on the rest of the body. Thus, our investigators study diseases like AIDS and diabetes, both of which have conspicuous oral signs and complications. We also study diseases more common in women, such as osteoporosis and Sjögren's syndrome--a condition in which the salivary and tear glands are destroyed. In general, our goals for the nineties include research aimed at improving the oral health of all individuals at high risk because of medically compromising or handicapping conditions or because of limited ability or access to care--groups that include the elderly and members of racial and ethnic minorities.

In supporting this broad research agenda, NIDR has emphasized investigator-initiated research project grants and promoted the use of comprehensive research centers in which multidisciplinary teams of investigators conduct basic and clinical research in areas of high priority. We have diversified the Institute's network of research centers, increasing basic research capacity as well as adding new clinical and categorical centers.

We have also increased the research capacity of dental schools through expanding the research centers program and developing novel training programs for careers in science through the Dentist-Scientist Program. Today, there are more research-intensive dental schools than in the early 1980s, and the number of ably trained researchers has increased.

Finally, strengthening the partnership with the practicing profession and the public became a special goal for the Institute, placing emphasis on science transfer and communication. The Institute implemented a variety of means to convey research findings from the laboratory to the profession and to the public. NIDR launched a series of continuing dental education conferences for practitioners entitled "Scientific Frontiers in Clinical Dentistry," attracting hundreds of practitioners from throughout the country. Recently we established the National Oral Health Information Clearinghouse as a resource center for educational materials aimed at "special needs" patients whose medical conditions compromise oral health. Working with voluntary organizations like the National Alliance for Oral Health and the American Fund for Dental Health, we are now engaged in national oral health promotion campaigns.

It is difficult, of course, to give justice to the many activities that have filled these almost 12 years of my tenure at the NIDR; but I leave with the satisfaction of knowing that there are people and programs in place, and that both are well poised to meet the challenges of the future. The future of dentistry is more exciting than ever; it is a future in which the oral health care provider will be prepared to diagnose, treat, and ultimately prevent the entire range of oral health problems including oral infections, oral cancers, chronic orofacial pain, joint problems, salivary gland dysfunctions, and disorders of taste, smell, swallowing, and others.

SMALL GRANTS PROGRAM

Mr. Stokes: Under the "Other Research" budget mechanism, the Institute has included funds to support "young and minority research grants." How much of the $3,178,000 included in this budget mechanism would you allocate for this initiative?

Dr. Löe: We estimate that in FY 1995 nearly 80 percent--or $2.5 million--of these funds will be used to support the small grants program, which is encouraging young and minority investigators.

ORAL CANCER

Mr. Stokes: What is NIDR doing to address the problem of oral cancer, especially in relation to ethnic and racial minorities where the problem is more severe?

Dr. Löe: Several of the NIDR-supported planning grants for Regional Research Centers for Minority Oral Health are conducting studies to identify molecular events correlated with oral cancer that may account for a higher survival rate for Caucasians (54 percent) than for African Americans (33 percent). Another center is comparing exposure to alcohol and tobacco with expression of cancer-causing genes in the oral tissues of African Americans and Caucasians.

In collaboration with the National Cancer Institute (NCI) we are supporting a study in Puerto Rico where the oral cancer incidence is unusually high. Investigators are evaluating contributing factors, such as tobacco and alcohol, and the presence of human papillomavirus infection, as well as dietary and genetic factors.

Other studies suggest that nutritional and genetic factors may also play a role in oral cancer, especially in patients who use alcohol and tobacco. These studies are exploring whether vitamins A and C and beta-carotene may be key nutrients in the prevention or amelioration of oral cancer.

In addition NCI, NIDR, and Major League Baseball are campaigning to stop the smokeless tobacco habit popular among young men, particularly Native Americans. Posters, a brochure, and a videotape highlighting the hazards of "spit" tobacco are among the materials that have been produced and widely distributed to minor and major baseball teams and high schools.

BIOMATERIALS RESEARCH

Mr. Stokes: Are we making any real progress in the development of biomaterials to use as alternatives to mercury amalgams for fillings?

Dr. Löe: NIDR research on biomaterials has led to a mercury-free substitute for dental amalgams. While there is no scientific evidence that mercury, in the amount used in fillings, is harmful, the new prototype metal filling material developed through NIDR support of research at the National Institute of Standards and

Technology avoids the use of mercury completely. Several patent disclosures and a continuation to the original patent have been filed, and a Cooperative Research and Development Agreement (CRADA) has been negotiated with industry to commercialize the technology.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress with respect to the treatment of a variety of diseases and disorders. What diseases and disorders, under the purview of your Institute, would benefit from advances in this research area? What opportunities for further advancement are on the horizon in gene therapy as it relates to research underway at your institute? To what extent will these opportunities be pursued at the FY 1995 budget request level?

Dr. Löe: Scientific progress has made gene transfer technology more "user friendly," enabling it to be applied to both acquired as well as inherited conditions. Indeed, most conditions under NIDR's purview will benefit from this technology.

NIDR supports both extramural and intramural gene transfer research, which has already resulted in significant achievements. For example, extramural scientists have devised a way to transfer a type of gene that can destroy cancer-causing genes derived from papilloma viruses. This type of therapy is effective in the laboratory for killing oral cancer cells with these virus genes. Intramural scientists have used recombinant adenoviruses to transfer foreign genes into salivary glands of laboratory animals. They have now begun to repair glands damaged by autoimmune disease or radiation.

In other research, our scientists are working on ways to transfer genes into brain cells. These genes can make chemicals that can be used to relieve chronic pain such as that associated with temporomandibular disorders and various neuropathies. Gene transfer to salivary glands also has another novel use: getting glands to make chemicals with pharmaceutical effects. This approach is being used in collaborations between intra- and extramural scientists to treat upper GI tract infections such as candidiasis in immune-suppressed patients as well as to disrupt dental plaque formation, thereby potentially reducing tooth decay and gum disease.

These and other scientific opportunities in gene therapy will continue to be pursued in FY 1995 at an estimated level of $950,000.

GENE THERAPY IN AIDS RESEARCH

Mr. Stokes: The Congressional Justification mentions some experiments using the salivary glands for gene therapy. Would you describe this work and how it relates to your research program on AIDS?

Dr. Löe: NIDR investigators have made major contributions to understanding how the salivary glands secrete saliva, and they have identified the genes and the genes' protein products in saliva that help protect the oral tissues from infection. One of the advantages of salivary gland research is that the glands are readily accessible.

In their recent experiments, the investigators inserted a gene for a salivary protein called histatin directly into the salivary gland ducts of rats. Not only was the gene successfully inserted into the duct cell nuclei, but the protein product was expressed and secreted into the mouth. This particular protein has potent anti-yeast properties and normally functions in our mouths to prevent the yeast infection, candidiasis. People who are immunosuppressed or infected with HIV frequently develop severe and painful candidiasis. If we can demonstrate that the gene-insertion technique that worked in rats can be applied to human patients, we might be able to provide a very potent therapy using a natural anti-yeast agent that would be slowly and continuously released in the mouth.

MINORITY RESEARCH INITIATIVES

Mr. Stokes: How does the Institute determine which minority research initiatives to fund? Are funds set aside to fund targeted minority research initiatives?

Dr. Löe: Funding of minority research initiatives, like those of other initiatives, is based upon technical merit and programmatic relevance. The Institute has maintained a comprehensive approach to the development of policies and programs to advance participation of minorities and improve their oral health, making extensive use of its standing advisory committees, the National Advisory Dental Research Council (NADRC) with its Subcommittee on Minorities Activities, which works closely with the NIDR internal Minority Activities Committee; and the Dental Research Program Advisory Committee. On occasion, ad hoc groups of nongovernment experts are convened, as was the case in developing the Regional Research Centers for Minority Oral Health initiative, where input from each minority subgroup was essential. Scientific assessment of applications is conducted by the customary NIH initial peer review system, either through the Division of Research Grants' study sections or by the Institute's initial review committees. Secondary review is provided by the NADRC. In the case of minority supplements to research grants, assessments are made by an internal NIDR extramural Scientific Review Committee.

It is the usual practice in the NIDR to set aside funds for minority research initiatives, since these, like other initiatives, include the use of Requests for Applications.

Mr. Stokes: How many minority research initiatives are currently funded by the Institute? Are funds set aside to support each of them? Explain.

Dr. Löe: In FY 1993, NIDR funded 40 research projects specifically targeted to minorities for $7.3 million. These projects included studies of periodontal disease and caries in ethnic minorities, oral cancer in African Americans and Hispanics, the oral health consequences of diabetes in Pima Indians, genetic epidemiology and mapping of oral clefts in Asian populations, and the natural history of HIV infection in minority women and intravenous drug users. Funding for this research is the result of the peer review process; therefore, specific dollar amounts are not set aside.

In addition, the Institute supported $3.5 million in minority health and assistance programs with set-aside funds, including:

- **Regional Research Centers for Minority Oral Health (RRCMOH)** - Six developmental, 3-year grants for a total of $2.1 million were awarded in FY 1993 to consortiums of minority dental schools or schools serving large minority populations in Virginia/District of Columbia, California, Tennessee/Alabama, Connecticut/New Jersey, New York/Boston, and Texas. These collaborations, now in their second year of support, were initiated in an effort to improve minority health through research, increase the number of minority research investigators, and enhance faculty development.

  In January 1994, a Request for Applications announcing the second phase of this program was issued. The Institute expects to award three grants for full-scale research centers in FY 1995.

- **Minority Research Supplement Program** - These administrative supplements are available to all principal investigators who hold NIH research grants, for the support and recruitment of underrepresented minority scientists and students. In FY 1993, NIDR support totalled $1.3 million for this program.

- **Minority Biomedical Research Support (MBRS)** - In FY 1993, NIDR supported $77,000 in MBRS awards. These grants are designed to strengthen the biomedical research and research training capability of ethnic minority institutions.

- **Minority Access to Research Careers (MARC) Undergraduate National Research Service Awards (NRSA) grants** - In FY 1993, NIDR funded $35,000 in MARC awards. These grants enable minority institutions to award NRSAs for research training in the biomedical and behavioral sciences to minority individuals of their choice.

Mr. Stokes: I understand that a number of institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. Does the NIDR make minority supplement awards, if not, why not? And, if so, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Löe: The NIDR has participated in the minority supplement mechanism of research support since its inception at the NIH, over 4 years ago. The NIDR ranks second among the 19 Institutes in the percentage of funding allocated to minority supplements. In FY 1993, 33 awards were made at a cost of more than $1.3 million. The number of recipients who have completed a supplement experience is too small to evaluate their success, especially because they range in experience from high-school students to university faculty. However, we do have a system in place for monitoring their progress; this system should provide appropriate evaluation within a few years.

MINORITY EMPLOYMENT

Mr. Stokes: Within the Dental Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In FY 1993, how many African Americans were at the GS-15 and above level?

Dr. Löe: The NIDR has two African American employees at the senior levels. One individual is the Chief of the Animal Care Unit in the Intramural Research Program; the other is Chief of the Health Assessment Section in the Epidemiology and Oral Disease Prevention Program. Both individuals held these positions in FY 1993 as well.

PAIN IMAGING

Mr. Stokes: What progress is the Institute making in neuroimaging as it relates to the brain's response to pain? What are the implications of this research?

Dr. Löe: NIDR intramural scientists are using state-of-the-art equipment available at the NIH Clinical Center to study what parts of the brain are affected by pain. One of the surprises of the PET scan studies, which use radioactive tracers to delineate the areas of the brain most affected by pain, is how much of the brain is affected. Not only is there activity in the area that registers the anatomical site where the pain is felt, but also large areas associated with emotion. In the case of patients with chronic pain, these studies are providing evidence of long-term changes.

In another technique, called functional magnetic resonance imagery, portions of the outermost surface of the brain--the cortex--show dramatic instant-to-instant changes in response to the onset and duration of a painful stimulus. These studies provide strong evidence for the complex, multidimensional nature of pain. They will surely add to our fundamental knowledge about the workings of the human brain and they may be useful in diagnosing and evaluating treatments of chronic pain conditions.

In other research, our investigators are testing new classes of drugs as analgesics. Some of these drugs are being evaluated in patients with particularly difficult-to-manage pain, such as occurs in reflex sympathetic dystrophy.

DENTIST-SCIENTIST PROGRAM

Mr. Hoyer: Dr. Löe, NIDR inaugurated a Dentist-Scientist Program some years ago to increase the numbers of clinically trained investigators conducting oral health research. I have strongly supported the program in its developing years, and I would like to know where it stands today. Have you been able to accomplish the program's goals?

Dr. Löe: The Physician Scientist Award for Dentists and the Dentist Scientist Award programs were established in 1984 and 1985, respectively. These programs were developed in response to documented declines in numbers of clinician scientists and were intended to prepare a cadre of competent scholars for careers in oral health research. To date, approximately 90 individuals have completed the programs and have accepted positions at more than 30 U.S. academic institutions, primarily dental schools. Although these individuals are relatively early on in their research careers, we are already seeing positive indications that, in fact, the graduates are pursuing successful careers in oral health research: virtually all graduates are employed by academic/ research institutions, and they are actively applying for and receiving research grant support from a variety of sources including NIH, universities, foundations, and industry. Currently we have 118 dentist-scientists in career development programs.

PAIN RESEARCH

Mr. Hoyer: The Congressional Justification mentions the use of new imaging techniques that show what happens in the brain when a person feels pain. What does that mean in terms of our understanding of pain and its control? What other advances has NIDR made in pain research recently?

Dr. Löe: NIDR intramural scientists are using state-of-the-art equipment available at the NIH Clinical Center to study what parts of the brain are affected by pain. One of the surprises of the PET scan studies, which use radioactive tracers to delineate the areas of the brain most affected by pain, is how much of the brain is affected. Not only is there activity in the area that registers the anatomical site where the pain is felt, but also large areas associated with emotion. In the case of patients with chronic pain, these studies are providing evidence of long-term changes.

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HEALTH CARE REFORM

Mr. Hoyer: Dr. Löe, how do you see oral health research contributing to health care reform?

Dr. Löe: Biomedical, behavioral, and health services research are critical components of any health care reform effort. Not only will the findings lead to improved health through the development of more efficient disease prevention and health promotion measures, but also more effective treatments will emerge. Research also will be needed to monitor health status, care utilization, and treatment to evaluate the outcomes of any health care reform programs.

Dentistry is already on record for having held the line on costs. As I mentioned during the hearings, dental costs have risen very modestly over the decade compared to medical and hospital costs. In fact our analyses indicate that from 1979 to 1989, Americans saved close to $40 billion in dental care costs--primarily because dental care is increasingly focused on prevention. Not only are we saving more teeth, and hence saving the costs of dentures, we are seeing fewer and smaller cavities in children and younger adults, which is good news for the long term. The key to our contribution to health care reform is continued emphasis on prevention research and also the development of better, more accurate, and earlier diagnoses of disease so that we can intervene when it is still possible to reverse the disease process.

We are also interested in risk assessment by searching for biomarkers of disease or risk for disease in saliva or other easily sampled oral tissues. The value of such biomarkers is that they can be used to screen for many conditions: genetic disorders, systemic diseases, infections (including HIV), levels of hormones, alcohol, drugs, prescription medications, and so on.

HISPANICS AND NIH

Mr. Serrano: Dr. Löe, as you know, I raised questions with Dr. Varmus this morning regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. You are on the lucky first panel, but the others will not be neglected.

First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Löe: The Institute continues to take positive steps to attract minorities, including Hispanics, to research training opportunities and job openings. Recently, for example, the Institute placed an advertisement in "Anuario Hispano 1994 Hispanic Yearbook" as a means to attract Hispanics to research training opportunities. As job vacancies occur, positions are advertised in Hispanic and other minority-specific publications, in science and health media, and through professional organizations. Particular attention is focused on certain occupations in which minorities are underrepresented, and specific recruitment strategies are undertaken, as outlined in the Federal Equal Opportunity Recruitment Program (FEORP) guidelines issued by the NIH and the Institute. NIDR staff are encouraged to participate in Hispanic conferences and seminars to share information about the various research opportunities available. Similar information is shared with members of the Institute's Public Advisory Committees, where Hispanics are represented.

Promotional consideration is accorded to all Institute employees, including Hispanics, in light of an individual's performance, growth in responsibilities, scientific excellence, or similar objective measurements, as appropriate for the position. The Institute fully supports the career development and advancement of all staff.

Mr. Serrano: Second, what percentage of your Institute's budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Löe: At this time, approximately 1.4 percent of the NIDR extramural research budget is specifically targeted to Hispanic health issues. It should be noted, however, that virtually all research in oral health has impact for Hispanics.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Löe: The NIDR is an active participant in an NIH program, Research Supplements for Underrepresented Minorities. Of 26 active NIDR supplements, nine are to students or investigators of Hispanic origin.

The NIDR supports a short-term summer research training program exclusively for ethnic minority dental students, which is held at the University of Rochester. Since inception of this program 6 years ago, over 50 percent of trainees have been Hispanic. Because of this success, we plan to fund four or five more similar programs this year.

NIDR support of Regional Research Centers for Minority Oral Health includes the University of Texas at San Antonio, which serves a large Hispanic community. The aim of the center includes enhancement of research skills of Hispanic faculty, as well as research targeted to improving the oral health of the Hispanic population.

The NIDR maintains networks with Hispanic institutions of higher education and other organizations, including the Hispanic Dental Association, to involve greater numbers of Hispanics in biomedical and behavioral research as well as on the Institute's Public Advisory Committees.

Mr. Serrano: Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Löe: The Institute, through its Regional Research Centers for Minority Oral Health, encourages maximum participation of Hispanic subjects in clinical studies, particularly when the disease disproportionately affects Hispanics. This is true for the center in San Antonio, Texas, whose patient population approaches 100 percent Hispanic, and for those in New York City and Los Angeles where more than 50 percent of the patient populations are Hispanic. In addition, the NIDR participated in the Hispanic National Health and Nutrition Examination Survey, providing funds to determine the oral health status of Hispanic Americans. Finally, the new NIH Guidelines for Inclusion of Women and Minorities will ensure proportional participation of Hispanics in clinical trials, which is likely to result in changes in health policies and standards of care.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators; how their success rate compared to the Institute's overall success rate; and whether there is an explanation for any disparity in these success rates.

Dr. Löe: First, it is important to note that ethnic/minority information on grant applications is not required by applicants, but is provided by them solely on a voluntary basis; consequently we receive some applications that do not carry this information. Furthermore, the definitions of minority sub-groups are subject to varied interpretations by applicants and therefore may not be technically accurate. With the limited information that we do have, however, we can verify that two of nine applications from Hispanic investigators were funded in FY 1993, for a success rate of 22.2 percent. This compares favorably with the overall success rate of 24.3 percent. As the NIDR's Regional Research Centers for Minority Oral Health and other minority initiatives reach maturity we expect the success rate of Hispanic investigators to improve.

WEDNESDAY, APRIL 20, 1994.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

HAROLD E. VARMUS, M.D., DIRECTOR

CLAUDE LENFANT, M.D., DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

PATRICIA A. GRADY, PH.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

MARVIN CASSMAN, PH.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Mr. SMITH. We have three more institutes today. You may proceed as you please.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Thank you, Mr. Chairman. Good morning. On my right, Claude Lenfant, who is the Director of the National Heart, Lung and Blood Institute. On my left is Dr. Patricia Grady, who is the Acting Director of Institute of Neurological Disorders and Stroke. On my extreme left is Dr. Marvin Cassman, the Acting Director of the National Institutes for General Medical Sciences. They will each make brief presentations to you. And then we will proceed with questions.

OPENING STATEMENT

Dr. LENFANT. Thank you, Mr. Chairman. I am pleased to present to you the programs of the National Heart, Lung, and Blood Institute. The diseases for which we are responsible constitute a huge public health problem and an enormous financial burden. For example, in 1991, the economic cost of heart, lung, and blood diseases was about $269 billion. In addition, the conditions with which we are involved, account for approximately half of the deaths in the United States.

Despite these worrisome statistics, I come as I have before, to bring you some very good news, and to alert you at the same time to an emerging important problem. The good news is that the death rate from cardiovascular diseases has steadily declined since the mid-1960s.

Looking at the entire U.S. population in the last 12 years alone, as you can see here on this chart, the decline in death rate from coronary heart disease, which is the most important of our conditions, has been 25 percent and for stroke it has been just about the same.

There are many other examples of very significant achievements. For instance, let me mention the case of sickle cell disease. Several decades ago many of the patients were dying in their late teens. Today, the life span has increased considerably and, indeed, patients with sickle cell disease live into their 40s and their 50s.

PREVALENCE OF HEART DISEASE

So in the light of this good news, what is the problem that I want to bring to your attention? Mr. Chairman, as I just mentioned, we have reduced the death rates, but we have not significantly reduced the occurrence of the diseases that we are concerned with. So therefore today we have more Americans of all ages, all races and both genders, who suffer from these conditions. This is shown by the prevalence line that you see here on this chart; you can see that during the last 12 years there was an increase of approximately 33 percent in the number of people suffering with coronary disease.

So at the time we are all concerned with health for all, the burden is increasing and it will continue to do so unless we can first prevent the occurrence of the diseases we are concerned with. And second, that we can not only treat them, but cure the people who become ill.

OPPORTUNITIES

So where does that leave us? And do we have an answer to the question that I just mentioned? The answer I believe is, yes. Indeed, the effort of the last decade in basic research have given us the tools that can be applied to our problems. Today we have more opportunities and promises for success than ever before and I would like to mention some examples of some very exciting work that is going on at the present time.

One is on hypertrophic cardiomyopathy, which I mentioned in my written statement. It is an inherited disease which often causes sudden death, particularly in young athletes. Recent studies at the molecular level combined with new clinical tests enable us to characterize the disease and to predict its severity. As a consequence, very effective treatments have been developed to permit a near normal life for many of the patients with this condition.

Another example is asthma, a common but complex respiratory disease. Recent studies have clearly established that asthma is caused by genetic determinants that are activated by environmental and other factors. And there is great optimism that very soon we will find a way to prevent and hopefully cure this condition.

GENE THERAPY

Finally, as the last example, I would like to mention some of our work on gene therapy. Gene therapy is making remarkable headway. Our Institute, as you know, has pioneered the work on gene therapy of inherited diseases such as some immune deficiencies, cystic fibrosis, and hemophilia.

Today we are conducting research to apply gene therapy to treat acquired conditions. One example is acute respiratory distress syndrome, which is a sudden respiratory failure. This is a very common condition which is fatal in about half of the cases. Recent work has demonstrated that by transfecting genes we can interrupt the process that is causing this problem.

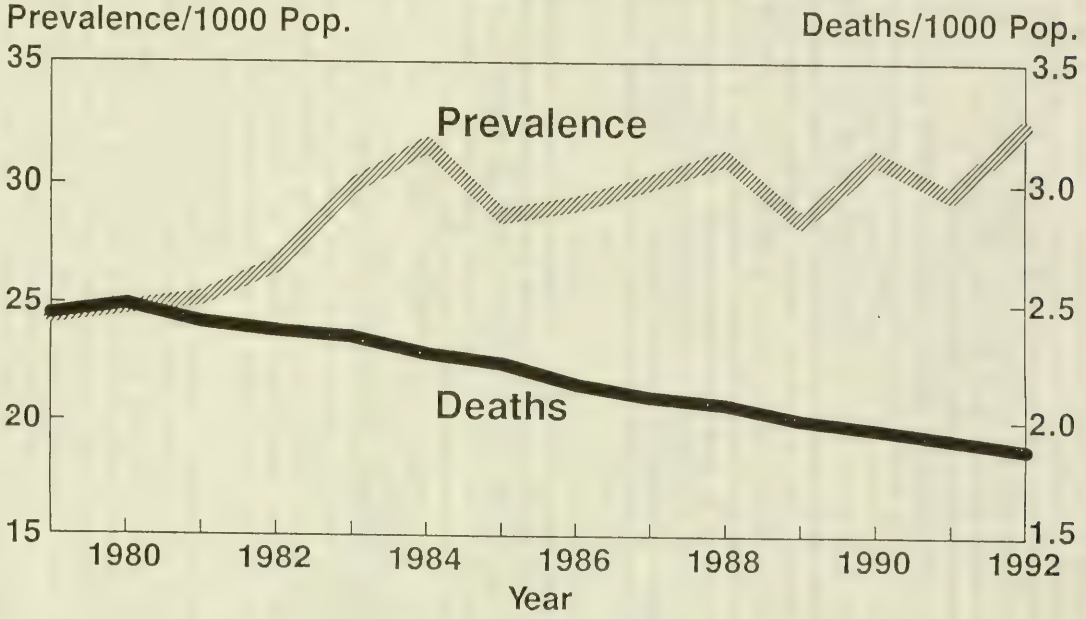
Let me mention another example where gene therapy begins to play a very significant role. Heart attacks, the one which is depicted on the chart I showed, usually results from an obstruction of the coronary arteries. The treatment to that, as you know, is either surgery or angioplasty; angioplasty is becoming the treatment of choice for many of these patients. The problem is that angioplasty itself may trigger a proliferation of cells inside the vessel which, in turn, will cause reobstruction of the vessel. What we have recently found is that we can apply genetic material within the artery to block the cell proliferation. Now, considering that approximately 400,000 angioplasties are performed in this country each year, and that about half of this number reobstruct, the impact of this work that I have just mentioned, if successful, would be enormous.

So to summarize, Mr. Chairman, I want to underscore that the Institute is facing big public health problems. However, our research programs are successful. And my way to look at it is not “do we know what to do to solve our problems?” I think we know what to do. The question rather is how fast can we do it.

Mr. Chairman, the budget request for the Institute is $1,266,961,000.

[The prepared statement and biography of Dr. Claude Lenfant follows:]

Prevalence and Mortality from Coronary Heart Disease; U.S., 1979-92



DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Heart, Lung, and Blood Institute

I am pleased to address this committee once again on behalf of the National Heart, Lung, and Blood Institute (NHLBI). Now in its forty-sixth year, the Institute came into being at a time when elation over the public health miracle wrought by control of infectious disease was rapidly giving way to concern about the chronic diseases that stalk people as they grow older. It became apparent that enjoying a long and healthy life depended to a great extent on how well a person's heart, blood vessels, lungs, and blood functioned. That remains true today. Despite remarkable medical advances that have reduced death rates dramatically, more than half of Americans who died last year succumbed to diseases that the NHLBI is working to treat, cure, or prevent. To meet this continuing challenge, the Institute conducts a broad-based program that emphasizes acquisition of fundamental knowledge; testing, evaluation, and validation of promising approaches derived from that knowledge; and transfer of findings to practice. The advances highlighted below attest to the success of this strategy.

The Institute supports a wide range of studies on the structure and function of the heart muscle, some of which focus on hypertrophic cardiomyopathy (HCM), an inherited heart defect that has made headlines as the cause of sudden death in apparently healthy young athletes. In a collaboration that exemplifies the benefits to be gained by close interaction between basic and clinical research, a group of NHLBI intramural investigators has integrated clinical and molecular efforts in such a way that laboratory data guide and motivate clinical research, which in turn provides material and direction for new basic studies. This research has demonstrated, for example, that use of a dual chamber pacemaker offers a therapeutic alternative to surgery that is at least as effective, less expensive, and safer for some patients. Other studies involving several hundred patients have shown that electrophysiologic (EP) tests are valuable in gauging the probable consequences of HCM in adults and children, because they enable identification of potential arrhythmic causes of sudden death and fainting spells. EP studies not only yield information on the prognosis for a given patient, but also may indicate therapeutic strategies to reduce risk.

A variety of genetic mutations can cause HCM, and are associated with different clinical characteristics and prognoses. For example, two mutations have been identified that seldom result in disease and have a benign prognosis, and a third mutation has been found to cause disease in 100 percent of affected persons and to confer a high risk of sudden death. The availability of molecular markers has made it possible to perform preclinical diagnosis of HCM in children. Thus, application of basic genetic studies to HCM and the discovery that HCM is linked to a particular gene that governs the heart muscle have transformed what was a disease defined only by its clinical manifestations into a molecular disease, and set the stage for improved clinical management and genetic counseling of patients.

The success of this approach illustrates not only benefits to be gained from the marriage of basic and clinical research, but also the exceptional promise of the discipline of molecular biology. Recognizing the vast potential of this new field, the Institute has taken a number of steps to orchestrate a program aimed at rapid yet deliberate progress.

Considerable headway is already being made with respect to cardiovascular, pulmonary, and hematologic diseases caused by a single defective gene. To guide and advance its research efforts in this area, the Institute convened a Working Group on Gene Therapy Approaches and Resources for Heart, Lung, and Blood Diseases to examine ways in which existing knowledge could be used to devise effective methods of genetic therapy for such diseases. The Working Group's recommendations have already led to development of three new programs focused, respectively, on cystic fibrosis, hemophilia, and sickle cell disease. The sickle cell initiative, which takes advantage of innovative ways of introducing modified hemoglobin genes into bone marrow cells, is expected to produce results applicable to other hereditary hemoglobinopathies such as Cooley's anemia. These efforts promise to revolutionize our mastery over diseases that have plagued generations of families.

Even more exciting is the potential application of molecular genetic approaches to multifactorial diseases, such as high blood pressure and asthma. These diseases represent a new frontier because they do not follow the classical laws of genetics and they involve special medical and societal challenges. To identify scientific priorities in this area, the Institute formed an Expert Panel on Genetic Strategies for Heart, Lung, and Blood Diseases, which recently produced a Master Plan that describes research opportunities and implementation strategies. Several new research initiatives have already been developed pursuant to this plan, including a shared support facility for mammalian genotyping and collaborative programs to delineate the major genetic determinants of high blood pressure and asthma. Although successful exploitation of this approach will demand patience, flexibility, and hard work, we believe it offers extraordinary potential for presymptomatic diagnosis, carrier detection, primary prevention, and cure of complex diseases. Such efforts now assume greater importance than ever in light of this country's growing interest in containing health care costs while ensuring that the benefits of modern medicine are available to all Americans.

Clinical trials are the most reliable approach to validate new knowledge and determine whether it is ready for wider application. These studies enable the Institute to assess the efficacy of therapeutic or preventive strategies; to compare outcomes among persons of various gender, racial/ethic, or health status; and to address such issues as health quality of life and cost-effectiveness. For instance, a new clinical trial, Antiarrhythmics Versus Implantable Defibrillators, will determine whether patients resuscitated from life-threatening arrhythmias fare better with an implantable cardiac defibrillator (ICD) or with the drugs amiodarone or sotalol. Findings will provide a valuable guide to managing patients with serious ventricular arrhythmias. Furthermore, by improving the ability to identify subgroups of patients likely to benefit from the ICD, the new information will facilitate appropriate use of this expensive new procedure. Another trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack, will compare the effectiveness of four classes of antihypertensive drugs in preventing heart attacks and cardiovascular deaths in older persons. The study will enable us to distinguish differences between black and white patients, and between women and men, in their response to treatment, and to compare the effectiveness of costly newer drugs, such as ACE inhibitors, with that of inexpensive older drugs, such as diuretics.

The NHLBI currently supports five major technology transfer activities: the National High Blood Pressure Education Program, the National Cholesterol Education Program, the National Asthma Education and Prevention Program, the National Heart Attack Alert Program, and the Obesity Education Initiative. Although these programs consume only a small fraction of the Institute's budget, they are among its most important efforts because they play such a visible role in bridging the gap between fundamental research findings and health-related behavior. Their influence ranges from updating standard medical practices in the United States to changing the everyday habits of its citizens. Not only do they facilitate the most effective application of NHLBI research findings, but they also identify new research directions that demand exploration.

During the past year, the National Asthma Education and Prevention Program (NAEPP) developed a broad-based strategy with respect to asthma prevention, focused on persons, especially minorities, with undiagnosed asthma. A mass media campaign has been implemented nationally to create greater awareness of asthma's warning signs and to encourage people who experience them to seek treatment. Reducing the burden of asthma in young children is the goal of several new school-based initiatives. "Asthma Awareness: A Curriculum for the Elementary School Classroom" and a videotape for teachers on managing asthma are being distributed widely to help both teachers and students learn about how they can help schoolchildren with asthma. The National School Boards Association and the NAEPP are developing a joint policy statement that will encourage schools to assure convenient and prompt access to asthma medications, and give appropriate consideration to student self-administration. A new NHLBI research initiative, "Interventions to Improve Asthma Management and Prevention at School," will develop and evaluate innovative programs that incorporate all components of a comprehensive school health program. Applications from schools that serve minority populations will be encouraged, given the greater severity of asthma and the higher risks for school failure among minority children.

As the country moves forward with health care reform, we believe the spectrum of activities conducted by the NHLBI will expand the range of choices open to policymakers and facilitate achievement of the nation's public health objectives.

Mr. Chairman, the FY 1995 NHLBI budget request, excluding the amount for AIDS related research, is $1,266,961,000. I would be pleased to answer any questions the committee may have.

LENFANT, CLAUDE, M.D.
Director, National Heart, Lung,
and Blood Institute, NIH

October 12, 1928, Paris, France

Education: B.S., University of Rennes, France, 1948. M.D., University of Paris, France, 1956.

Professional History: 1957-1958, Research Fellow, University of Buffalo, New York. 1958-1959, Research Fellow, Columbia University, New York. 1959-1960, Assistant Professor of Physiology, University of Lille, France. 1961-1965, Clinical Instructor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1966-1967, Clinical Assistant Professor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1968-1971, Associate Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1970-1972, Acting Associate Director, Collaborative R&D Program, National Heart and Lung Institute, NIH. 1970-1972, Associate Director for Lung Programs, National Heart and Lung Institute, NIH. 1971-1972, Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1972-1980, Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH. 1981-1982, Associate Director for International Research, NIH. 1981-1982, Director, Fogarty International Center for Advanced Study in the Health Sciences, NIH. 1982-Present, Director, National Heart, Lung, and Blood Institute, NIH.

Professional Organizations: Association of American Physicians, American Society for Clinical Investigation, American Physiological Society, American Federation for Clinical Research, French Physiological Society, International Federation for Medical Electronics, American Society of Zoologists, Society for Experimental Medicine and Biology, Undersea Medical Society, New York Academy of Science.

Honors, Awards: Thesis Prize, University of Paris, France, 1956. Commendation Tohoku Medical Society, Sendai, Japan, 1973. Superior Service Honor Award, DHHS, 1974. Regents' Professor, University of California, Los Angeles, 1975. Testimonial Dinner, American Thoracic Society, 1979. Honorary Fellow, American College of Chest Physicians, 1979. Honorary Professor, National Yang-Ming Medical College Taipei, Taiwan, 1980. Honorary Professor, Universidad Peruana Cayetano Heredia, Lima, Peru, 1981. Senior

Executive Service Performance Award, 1982. Elected Institute of Medicine, National Academy of Sciences, 1983. American Heart Association Scientific Councils' "Distinguished Achievement Award," 1983. Senior Executive Service Performance Award, 1983. Honorary Fellow Council on Clinical Cardiology - American Heart Association, 1984. Senior Executive Service Performance Award, 1984. Forrest M. Bird Contributory Award, American Respiratory Therapy Foundation, 1985. Senior Executive Service Performance Award, 1985. Presidential Meritorious Executive Rank Award, 1987. Elected Honorary member, Royal Society of Medicine, England, 1988. Honorary Doctor of Science, State University of New York, Buffalo, 1988. Elected member USSR Academy of Medical Sciences, 1988. Cystic Fibrosis Foundation "Breath of Life" Award, 1988. Elected Honorary Member - French Cardiology Society, 1989. Senior Executive Service Performance Award, 1989. Brotherhood Award - Association of Black Cardiologists, 1990. Appointed, Board of Governors, US-Israel Binational Science Foundation, 1990-1993, Senior Executive Service Performance Award, 1990. Presidential Distinguished Executive Rank Award, 1991. Elected Fellow, Royal College of Physicians (London, England), 1992. Senior Executive Service Performance Award, 1992. 1992 Federal Executive of the Year Award. Elected member, French National Academy of Medicine, 1993. Surgeon General's Exemplory Award, 1993. Senior Executive Service Performance Award, 1993. Special Recognition Award - American Academy of Allergy and Immunology, 1994.

Authorship, Editorship: Author or Co-Author of 200 scientific publications Served on Editorial Boards of: Am. Journal of Physiology; Journal of Applied Physiology; Respiratory Physiology; Am. Review of Respiratory Disease; Undersea Biomedical Research; Proceedings of Society for Experimental Biology and Medicine; Revue Francaise des Maladies Respiratories; Journal of Applied Physiology; Respiration, Environmental and Exercise Physiology; Am. Journal of Medicine; Continuing Education for Family Physicians; Executive Editor of 74 volumes for monograph series, "Lung Biology in Health and Disease."

OPENING STATEMENT

Dr. GRADY. Good morning Mr. Chairman and Members of the committee. Over 600 neurological disorders can affect the brain and nervous system resulting from trauma, genetic defects, infections, environmental factors, tumors or inadequate blood supply leading to death or disability. These range from the very highly prevalent disorders such as stroke, the third leading cause of death in the United States, and trauma, the leading cause of death in Americans under 45 years of age, to the very rare genetic disorders.

An estimated 25 percent of all genetic disorders affect the nervous system. Permanent neurological disability affects 50 million Americans at a cost to the Nation of $400 billion per year.

NINDS serves as a catalyst through the support and conduct of research to understand, prevent and cure, and find treatments for neurological disorders so that time and resources are utilized for the maximum benefit. Until very recently there was little hope of finding a cause or a cure for many of these disorders. Some of the symptoms could be decreased, but the underlying disease process remained untouched.

Largely as a result of successful investments in basic research, that situation is changing. Pioneering examples of this new era include methods to prevent stroke, enzyme replacement to reduce the course of inherited metabolic disease and new treatments for multiple sclerosis, spinal cord injury and epilepsy.

Advancements made with NINDS support are translated into benefits for patients, families, and society in several ways. Let me list a few examples.

Preventing stroke. An estimated 20,000 to 30,000 strokes can be prevented each year with the use of aspirin or warfarin in patients with atrial fibrillation—irregular heartbeat. Eliminating unnecessary extracranial-intracranial bypass surgery, with a reduction in surgery of 80 percent, has produced an estimated savings of $22 million a year to the Nation, not to mention the personal cost of undergoing the unnecessary surgery.

Treating spinal cord injury. The first-ever treatment to decrease disability from spinal cord injury was discovered by NINDS scientists using a drug within the early hours following injury. This finding grew out of early basic studies using animal models.

RESEARCH OPPORTUNITIES

Today's research opportunities that will help us to further extend the benefits of neurological research include development of gene-based therapies for both genetic and nongenetic disorders, the clinical use of enzymes and other factors normally found in the healthy nervous system to help fight disease, and uncovering mechanisms that play a role in neurological disorders as diverse as Huntington's disease, Parkinson's Disease, epilepsy and stroke.

These advances are made possible because, for the first time in history, we have the tools to look at the living brain to identify and study the components of the nerve cells.

From the discoveries that are made, we can say, for instance, that this is the gene that is causing someone's seizure or we can say this is the treatment that will prevent a second stroke from happening. Some of the treatments that scientists are working on today sound rather simple—the use of aspirin, reducing body temperature—but the research must be carried out to determine what will be beneficial and for which patients it will be beneficial. Again, in the role of catalyst there is much that NINDS has done and can do.

Many findings are now pointing the way towards possible clinical advances. One example is the support of clinical trials to prevent and treat stroke. This is an area that addresses minority issues related to minorities and women. A new trial has been undertaken to learn whether estrogen can prevent a recurrent stroke in postmenopausal women.

In the past year, NINDS has established four pilot centers for the study of neonatal brain injury and research in related areas. Recent important breakthroughs showing that the use of indomethacin decreases the incidence and severity of brain hemorrhages in low birth weight infants came out of such centers.

Intramural and extramural efforts are resulting in an improved understanding of the causes of epilepsy and leading to new treatments. Research on the formation of myelin, the major component insulating the cells of the nervous system, will have important implications for demyelinating disorders such as MS and many others.

The knowledge of the elegant structure and operation of genes within the nervous system continues to grow, paving the way for new breakthroughs. The first gene for a neurodegenerative disorder of adult life was identified last year by NINDS-supported scientists, the gene for familial amyotrophic lateral sclerosis, Lou Gehrig's disease. This gene codes for superoxide dismutase, which is an enzyme that neutralizes free radicals—free radicals have been implicated in a number of other neurological disorders, including Parkinson's disease and secondary effects of traumatic brain and spinal cord injury.

Further, NINDS intramural scientists have obtained encouraging results in the first clinical evaluation of a genetic therapy for brain tumors. Other NINDS scientists plan to launch the first gene therapy trials for Gaucher's disease, a rare disorder. NINDS will also encourage efforts in gene therapy for Duchenne's muscular dystrophy and has joined with NIDDK to encourage new methods of gene therapy for inherited metabolic disorders.

We have much work to do to fulfill the hope of millions of Americans afflicted with or at risk for neurological disorders. We in the neurosciences and the neurological community will continue to work as hard and as fast as we can within the limits of our scientific imaginations, which are boundless, and the fiscal constraints, which are a reality.

Mr. Chairman, the fiscal year 1995 budget request for this institute is $630,440,000. I would be pleased to answer any questions that you might have.

[The prepared statement and biography of Dr. Patricia Grady follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) is the lead Federal agency for research on the normal function of the brain, spinal cord, and peripheral nerves, and the diagnosis, treatment, and prevention of neurological and neuromuscular disorders. Over 600 disorders affect the nervous system, as a result of genes, trauma, infections, environmental factors, tumors, or inadequate blood supply. For example, stroke is the third leading cause of death in the U.S. An estimated twenty-five percent of all genetic disorders affect the nervous system. Permanent neurological disability that restricts daily activity affects about 50 million Americans at a cost to patients, families, and society of $400 billion each year. Until very recently, there was little hope of finding the cause or a cure for most neurological and neuromuscular disorders, but that situation is changing. Pioneering examples of this new era of medicine include methods to prevent stroke, enzyme replacement therapy to reverse the course of an inherited metabolic disease, and the first-ever treatments to affect the course of multiple sclerosis and spinal cord injury. Neurological research efforts will continue to benefit Americans through improved understanding of brain disorders and the development of a variety of prevention and treatment methods appropriate to different patient populations and methods to restore nervous system function.

Trauma is the leading cause of death in Americans under 45 years of age, and brain injury is a major factor contributing to this death rate. Economic costs associated with head and spinal cord injury are estimated at $35 billion annually. Research supported by NINDS includes a clinical trial to expand treatment options for recovery from spinal cord injury and basic laboratory studies of methods to replace nerve cells and restore function.

Prevention efforts against stroke encompass the prevention of an initial stroke--as well as recurrent stroke--and strategies to limit damage to the brain following a stroke. NINDS-supported clinical trials have demonstrated the effectiveness of warfarin, aspirin, and surgery to prevent stroke in selected patient groups. Clinical trials now underway will tell us whether these methods can be extended to other patient populations. A new study has also been undertaken to learn whether estrogen can prevent a second stroke in post-menopausal women who have already experienced a stroke. Ongoing treatment studies are examining several approaches including new agents that target the blood clotting process in an effort to restore or maintain blood flow, preserve function, and improve recovery. We also need to know more about risk factors for stroke and the impact of stroke among different populations within the U.S. Three epidemiological studies currently address that issue. Intramural stroke research includes a focus on finding why risk factors trigger stroke. In 1993, NINDS joined with voluntary organizations to issue guidelines on the emergency treatment of stroke. This year, NINDS plans to publish two brochures addressing patient education and stroke prevention.

Neurological disorders in children are especially tragic because of the early and lifelong impact on physical and social development and educational opportunities. NINDS supports and conducts a spectrum of studies with the common goal to determine what has gone wrong and how to correct neurological dysfunction in children. For example, recent findings from an epidemiological study show that twins are at higher risk for cerebral palsy--an important finding in view of the increasing numbers of multiple births. Research on brain injury in the newborn includes a focus on bleeding in the brain, congenital hydrocephalus, and seizures. As a disproportionate share of minority infants are born early and underweight, they are at risk for many of these conditions as well as for language and motor disabilities. NINDS has established four pilot research centers in neonatal brain injury that involve laboratory, animal, brain imaging, molecular biology, and clinical studies to foster discovery of mechanisms of damage in the neonatal brain and therapeutic strategies appropriate to the newborn.

Research progress to understand and treat epilepsy, affecting approximately one percent of the population, depends upon abroad-based research program to improve diagnosis, treatment, and prevention strategies. NINDS supports and conducts basic laboratory studies to understand the mechanisms of cell signalling, since seizures are the visible result of nerve cells firing out of control. Through the Antiepileptic Drug Development (ADD) Program, compounds are identified and evaluated for their safety and effectiveness as anticonvulsants. It was through this program that the therapeutic potential of Felbamate, the first new epilepsy medication in fifteen years, was identified. Intramural and extramural efforts are expected to result in additional medical and surgical strategies to prevent seizures.

Selective degeneration and death of specific groups of nerve cells are the hallmark of several serious neurological disorders, including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and progressive supranuclear palsy (PSP). The first gene for a neurodegenerative disorder of adult life was identified in 1993 by NINDS-supported scientists when they discovered a defective gene that causes a type of ALS that occurs in a small number of families. Because the normal gene produces an enzyme that neutralizes the effects of free radicals, the discovery implicated free radicals as a culprit in ALS, and encouraged further study of their role in other neurological disorders. ALS research efforts include the pursuit of other genes implicated in ALS and studies of growth factors that may promote healthy function and prevent nerve cell death. Research efforts in Parkinson's disease and related disorders include studies of environmental and endogenous toxins, genetic predisposition, and altered chemistry within nerve cells. Ongoing treatment research in PD includes a clinical trial to evaluate the efficacy of fetal tissue implants, intramural studies of several novel approaches to improve symptom management and modify the course of the disease, and further clinical evaluation of deprenyl and antioxidants.

For some neurological disorders such as multiple sclerosis (MS), the problem is not in the neurons that transmit signals, but the myelin sheath that surrounds neurons to provide insulation that is affected. Although MS is believed to be an autoimmune disease, the precise factors that trigger MS are being addressed through research that may lead to strategies to treat and prevent the disease. These factors include genetic, viral, immune, and perhaps other unknown influences. Basic research to understand the formation of myelin, the major component of the insulating cells, should have applications to MS and other demyelinating disorders.

Patient studies of gene-based therapies for neurological disorders have been launched. NINDS intramural scientists, who are at the forefront of efforts to find new ways to deliver anti-cancer agents to the brain, have obtained encouraging results from the first clinical evaluation of a therapy to genetically modify brain tumor cells to make them vulnerable to antiviral medications. The technique, developed with scientists from NCI, will soon be expanded to patients with other types of brain tumor. Intramural scientists will soon launch the first gene therapy trials for Gaucher's disease. NINDS will encourage new efforts in gene therapy for Duchenne's muscular dystrophy and has also joined with NIDDK to encourage new methods of gene therapy for inherited metabolic diseases such as Batten disease. Recent progress in efforts to identify the cause of neurological disorders includes the genes for spinocerebellar ataxia and neurofibromatosis type 2, and success by intramural scientists to narrow the search for the gene for Niemann-Pick Type C disease. Increased efforts will explore the regulation and control of genes, which may lead to creative approaches to treat nervous system dysfunction.

More than half of the people infected with HIV develop neurological complications. NINDS scientists and grantees have identified many of the neurological manifestations of HIV in children and adults. Recently, collaborations with the AIDS Clinical Trial Group have been initiated.

Mr. Chairman, the FY 1995 budget request for this Institute is $630,443,000. I would be pleased to answer any questions you might have.

Patricia A. Grady, Ph.D.
Acting Director, National Institute of Neurological Disorders and Stroke

EDUCATION:

B.S.N., Georgetown University, Washington, DC ,1967; M.S., University of Maryland, Baltimore, MD, 1968; Ph.D., University of Maryland, 1977

PROFESSIONAL HISTORY: Acting Director, NINDS, 1993 to present; Assistant Director, NINDS, 1992-1993; Program Manager, Stroke and Brain Imaging, Division of Stroke and Trauma, NINDS, 1988-1992, Member, Rehabilitation Task Force leading to National Center for Medical Rehabilitation Research; NINDS Liaison to National Center for Nursing Research; Member, Advisory Group, NCMRR, NICHD, NIH representative to Interagency for Disability and Rehabilitation Research for Director, NIH; NINDS representative to Diagnostic Radiology Coordinating Committee; Research Assistant Professor, University of Maryland School of Medicine, 1980-1988; Director of Cerebrovascular Physiology Research Laboratory, Graduate Faculty Member; Lecturer, Maryland Academy of Sciences; Assistant Professor, University of Maryland, School of Nursing, (Joint Appointment)1979-1988, Consultant to Doctoral Program in Nursing (Ph.D); Instructor, University of Maryland School of Medicine 1977-1980; Research Associate, 1976-1977; Assistant Professor University of Maryland School of Nursing, 1970-1973, Acting Director, Senior Medical/Surgical Nursing Division; Director of Neurological and Neurosurgical Nursing Specialty; Member, Faculty Council; Chairperson, Student Health Committee; Student Government Advisor; Maryland State Nurses' Association Secretary; Instructor, University of Maryland School of Nursing, 1968-1970; Instructor, Washington Hospital Center School of Nursing, Washington, DC, 1966-1967, Director, Newborn Division, Maternal and Child Health Department

PROFESSIONAL ORGANIZATIONS: American Association for the Advancement of Science; American Academy of Neurology; Fellow, American Heart Association, Stroke Council; New York Academy of Sciences; Society for Neuroscience; Sigma Theta Tau National Honor Society; American Nurses Association; Council of Nurse Researchers; American Society for Professional and Executive Women; American Lung Association, Professional Education and Training Committee; Executive Board, Stroke Council, American Heart Association; Budget Committee, Stroke Council; Committee for the Development of Clinical Research in Stroke, Stroke Council, American Heart Association; National Advisory Voluntary Board of American Heart Association; Neurotrauma Society; Editorial Board, STROKE.

HONORS, AWARDS, FELLOWSHIPS:

Sol Greenberg Award for Leadership Ability and Clinical Excellence, Saint Francis Hospital School of Nursing; State Finalist for "Student Nurse of the Year," State of Connecticut; Dean's List, Georgetown University; Sigma Theta Tau National Honor Society; DHEW Graduate Traineeship--Division of Nursing for Master of Science Degree; NIH Predoctoral Fellowship for Doctor of Philosophy Degree; NIH Individual Postdoctoral Fellowship (Neuropathology); Elected Fellow, Stroke Council, American Heart Association; Executive Committee Member, Stroke Council, American Heart Association; Member, Search Committee, Editorship of Stroke, NIH Merit Award

OPENING STATEMENT

Dr. CASSMAN. Mr. Chairman, and Members of the committee, good morning. I am pleased to come before you to present the programs of the National Institute of General Medical Sciences, the NIGMS. Unlike most of the other Institutes at NIH, the NIGMS doesn't focus its interest specifically on disease entities nor on problems associated with different stages of life. Rather, its grantees work primarily on basic research, unraveling the fundamental processes of living organisms.

The priorities of the Institute are focused on individual research grants, which make up over 85 percent of our budget, and on the training of investigators, which accounts for most of our remaining funds. Included within this is a strong commitment to support of research in minority institutions and the training of minority scientists.

This basic research that the NIGMS supports has led directly to many applications of benefit to the U.S. public and to humanity in general. Indeed, the research supported by NIGMS bears witness to what may be the defining motto of the 20th Century—that knowledge is power. And the more fundamental the knowledge gained of nature, the more powerful it is as a tool to address the problems of mankind.

Nevertheless, one can ask, why do basic research? It is perfectly reasonable to ask why all of the research supported by taxpayers' dollars shouldn't be, "directed to practical aims or objectives" which is the definition of applied research. Dr. Varmus' opening remarks provided several examples of the way basic research contributed to important clinical outcomes.

I would like to amplify this a little bit further by providing a more detailed example of the way the fundamental understanding of a biological system can make possible progress on alleviating a human ailment, although neither the researchers involved in studying the disease, nor those doing the basic research had any indication until recently that the two were linked.

On this poster, copies of which you have on your desk, are representations of two lines of research which converged in 1993. This was developed by one of our staff, Dr. Peter Preusch. The items shaded in blue represent basic research and those in red are targeted research efforts.

On the right in blue is the trail of a set of basic research investigations concerning an enzyme which has already been mentioned by Dr. Grady, superoxide dismutase. The enzyme was discovered in 1969 by one of our NIGMs investigators and it proved to be a very interesting substance. It inactivated superoxide, a material which is normally produced in the cells and yet is highly toxic, and as Dr. Grady mentioned, it is one of the class of compounds called free radicals.

The circle that you see at the top of the blue boxes contains the logo of the NIGMS and it indicates those areas that were supported by our Institute.

In red is the targeted work that was directed to finding the gene for the inherited form of the disease, amyotrophic lateral sclerosis, Lou Gehrig's disease. We in fact had very little to do with this effort. It was primarily funded by the Neurology Institute, as you have already heard. But NIGMS did contribute indirectly to providing some of the tools that were required for this and on the left-hand side of the diagram you see a list of the variety of tools, techniques, methodologies that fed into the research efforts that were required to elucidate the nature of the gene.

In 1993, the two lines of research converged, when it was discovered that the mutations in the familial form of amyotrophic lateral sclerosis all occurred in a single gene for superoxide dismutase, or for SOD. Certain NIGMS-supported research had already been studying the structure of SOD and discovering the nature of the mutations in that protein. They were able to identify the locations in the enzyme where the defects occurred and evaluate some possible hypotheses for the malfunctioning of this enzyme.

One clinical investigator has said: “Up to now we had no idea of how to attack ALS. Now, we can begin to design therapy based on real science rather than just picking pills off the shelf.” A scientist that is heavily involved in studying the disease has said: There were over 3,000 papers in the literature on ALS and although a few raised the question of free radicals, quite frankly, it was not an area that had been investigated at all.”

If we had waited to study SOD until the link between it and the condition of ALS had become known, we would have 10 to 20 years more work to arrive where we are today with a clue as to where to look for a cure. It is important to recognize that the investigators supported by NIGMS couldn’t have known that their research would have helped in this way to explain this disease and the ALS people could not have predicted that SOD would be a factor in the disease.

We, however, could have been absolutely certain that a fundamental understanding of a biological material as important to the functioning of the cell as SOD would help in understanding and eventually in treating some disease. We just couldn’t have known which one. And that is really the answer as to why we shouldn’t just focus on research, “directed to practical aims and objectives,” because we don’t always know in what direction to look. And that is also the reason why what NIGMS does is essential to NIH and modern biomedical science.

As occurred with SOD and ALS, we can say with complete assurance that some fundamental discoveries that basic research will uncover will help in curing a whole range of diseases. However, we just can’t say which discoveries those will be.

Just as important as these tools and fundamental discoveries is the need to train the next generation of scientists. The Institute’s training programs are committed to support and help develop the best young talent for future careers in biomedical research. And in particular the NIGMS is committed to ensuring that all the talents and abilities of the people of this country are utilized by providing special opportunities for members of underrepresented minority groups. And in this regard, the NIGMS has placed major emphasis on its Minority Opportunities in Research, the MORE Program Branch.

I am pleased to announce the recent appointment for the first director of this branch, Dr. Clifton Poodry. He has been a faculty member of University of California Santa Cruz since 1972, with a strong research involvement in developmental biology. He is a Native American who has had a deep involvement in programs to increase the recruitment of minorities to science. We expect with his help and through the coordination afforded by the MORE Program to ensure that our funds for the support of minorities and minority institutions are optimally utilized.

We are also undertaking a reexamination of all of our programs, beginning with our training programs, to ensure that we adequately reflect the development of science and the needs of our grantees, as well as accommodating to the changes within government.

Mr. Chairman, the fiscal year 1995 budget for the National Institute of General Medical Sciences is $882,189,000. I would be pleased to answer any questions that you might have.

[The prepared statement and biography of Dr. Cassman follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Acting Director
National Institute of General Medical Sciences

Mr. Chairman and Members of the Committee, good morning. I am pleased to come before you to present the programs and progress of the National Institute of General Medical Sciences (NIGMS).

As you have heard on a number of occasions, the basic research supported by NIGMS lays the foundation for a broad range of disease-targeted studies. It also supplies the biotechnology and pharmaceutical industries with the steady stream of new knowledge they need for continued growth and vigor.

The past year has been an exciting one for basic research. Not only were many fundamental discoveries made, but the basic research roots of a number of important clinical advances were readily apparent. It is now clearer than ever that a single basic research finding can fan out into applications in many areas, and that a major clinical advance generally builds, pyramid-style, on years of basic research results. Stated another way, the results of basic research are certain to have practical applications in the future, often the very near future. The more fundamental a finding, the broader its application is likely to be. What cannot be predicted is what disease a given discovery will apply to, or what discovery is needed in order to learn more about a given disease.

Basic Research and ALS

Today, I would like to show you several examples of how years of NIGMS-supported basic research have resulted in stunning advances in our understanding of specific diseases. The first example is amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease. It was a little more than one year ago that scientists announced the discovery of a gene involved in a hereditary form of this disease. To their surprise, the gene turned out to encode an enzyme called superoxide dismutase (SOD), which was identified in 1972 by an NIGMS grantee doing basic studies on oxygen in biological systems. Over the next two decades, as outlined in the attached chart, NIGMS supported much of the fundamental acquisition of knowledge about the SOD enzyme that placed scientists in a position to apply the knowledge quickly once the link to ALS was made. If researchers had waited until a specific gene was shown to be involved in ALS before doing fundamental research on the enzyme the gene encodes, it might have taken another 10 to 20 years to get where we are today.

When the connection between ALS and SOD was discovered, scientists did not know how a defect in the enzyme could lead to the devastating neurological symptoms of the disease. So they turned to structural biology for answers. Two NIGMS grantees at the Scripps

Research Institute, Drs. John Tainer and Elizabeth Getzoff, had been studying the structure of the SOD enzyme for many years. They rapidly determined where mutations occurred in people with ALS, and found that the mutations disrupt the place where two SOD molecules join together to form an active enzyme. As a result, SOD is less able to perform its job of scavenging harmful forms of oxygen, called free radicals. When free radicals build up, neurological damage occurs.

The contribution of structural biology to providing a clue to the origin of ALS underlines one of NIGMS' guiding principles--that studies of biological structures at the molecular level will provide important clues to their function, and will point the way to new means of disease diagnosis, treatment, cure, or prevention.

Beyond its support of research on SOD itself, NIGMS also supported the development of a number of tools and techniques that were critical to research on both SOD and ALS. These same tools enabled researchers to track down genes involved in other diseases, such as Huntington's disease, cystic fibrosis, muscular dystrophy, and some types of cancer.

Basic Research and Cancer

Similar charts could trace the fundamental underpinnings of many other major clinical advances. For example, the discovery of a gene involved in a form of colon cancer--announced last December to great media attention--depended on years of NIGMS-supported basic research on how bacteria and yeast repair errors in DNA copying. The scientists who conducted this research wanted to know more about how cells work, but they realized that their studies would shed light on conditions, like cancer, in which cells do not work properly. What they could not predict at the outset was exactly how their results would be applied, but there was no doubt that there would be important applications.

Another case of years of basic research coming together to yield important new insights about disease is found in the story of p53. This protein plays a key role in half of all human cancers, including those of the breast and colon, as well as in the normal cell cycle of growth and division.

NIGMS grantees made many contributions to an understanding of p53's function. These were largely the result of studies of the cell cycle in such model organisms as frog eggs and yeast, which helped establish a link between cell cycle control and cancer.

We now know that under normal circumstances, p53 acts as a tumor suppressor by turning on the production of another protein, which keeps healthy cells from dividing prematurely. However, when the p53 gene is mutated, the stage is set for uncontrolled cell division and the development of cancer. In recognition of the tremendous surge in p53 research, Science magazine named p53 its 1993 Molecule of the

Year.

As a Science editorial on p53 noted, "The great excitement in this field and the understanding that has already been obtained are typical of basic research. A rather innocuous molecule is shown to play a key role in a basic body function. No possible clarification of its important role could have been obtained without the background knowledge of biochemistry, cell biology, and genetics that was also the product of basic research....Soon the diagnostic opportunities that basic research has made available will enable clinicians to diagnose certain cancers at a stage early enough for effective intervention to take place. Therapeutic drugs are likely to follow."

Basic Research and Drug Development

NIGMS also supports research at the forefront of drug development. Some scientists, such as Dr. Marvin Caruthers of the University of Colorado at Boulder, are pursuing rational drug design as an alternative to the current method of screening massive numbers of compounds for activity against a target molecule. Rational drug design builds upon basic knowledge in cell biology, genetics, biochemistry, and especially structural biology. It offers particular promise in the development of new drugs to fight AIDS.

A second area of exciting research is the design of tiny, hollow structures that can hold drugs, transport them to a site in the body, and release their contents. Dr. Julius Rebek of the Massachusetts Institute of Technology has created one such structure, which has the distinction of being self-assembling. He took his inspiration from viruses, which have evolved a similar mechanism for inserting their genetic material into a cell. Dr. Rebek's team is now working on developing a switch to open the hollow structure under certain conditions.

A different type of switch has been devised by another NIGMS-supported chemist, Dr. Stuart Schreiber of Harvard University. This switch could refine gene therapy by enabling patients to take a nontoxic pill to turn an inserted gene on or off--or, if the gene malfunctions, to destroy it. The approach might allow gene therapy methods to be used for diseases that are treatable with therapeutic proteins--such as insulin for diabetes--since it would allow the regulation of proteins produced in the body by genetically modified cells. This new technology is still at the test-tube stage, but it is causing great excitement and has already been licensed by a biotechnology company.

Nobel Recognition

A final example of the broad applicability of NIGMS-supported research is found in the Nobel Prize. NIGMS has compiled a remarkable record of supporting scientists for work that later wins the Nobel Prize. The most recent round of prizes was no exception: NIGMS provided research or training support to all four of the winners of prizes in chemistry and physiology or medicine. The work honored by the prizes--the discovery that genes are interrupted by noncoding sequences and the development of two important research tools, the polymerase chain reaction and site-directed mutagenesis--has truly advanced scientific knowledge and revolutionized the way in which research is done.

Training Tomorrow's Scientists

NIGMS helps our country maintain its scientific advantage by training many of the scientists who will conduct research in the future. These scientists require somewhat different training than was needed in the past. They need broader exposure to a variety of disciplines, to enable them to capitalize rapidly on new findings in many areas. These scientists are different in other ways, as well. More of them are female, and more of them are members of minority groups that have traditionally been underrepresented in biomedical research. NIGMS is committed to increasing the number of minority scientists and strengthening the research capabilities and science curricula of institutions with substantial minority enrollments. The Institute has placed major emphasis on its Minority Opportunities in Research Programs Branch, and I am pleased to announce the recent appointment of the first director of this branch, Dr. Clifton Poodry. Dr. Poodry, who is a Native American, has been a faculty member at the University of California, Santa Cruz since 1972. He has been deeply involved in programs to increase the recruitment of minorities to science careers, as well as in science education and research in the field of developmental genetics.

An Investment in the Future

In conclusion, I would like to quote from an article in the July 1993 issue of the Journal of NIH Research, written by Dr. Keith Yamamoto of the University of California, San Francisco, and Elizabeth Marincola, Executive Director of the American Society for Cell Biology. They state that "a strong and unswerving commitment to fundamental research is not the best way to guarantee continued progress in human medicine--it is the only way." I hope that my remarks today have reinforced this point--that basic research plays an important role in the health of the Nation and in technology development, and that it is one of the best investments we can make in our future.

Mr. Chairman, the fiscal year 1995 budget request for the National Institute of General Medical Sciences is $882,189,000. I would be pleased to answer any questions that you might have.

CURRICULUM VITAE
MARVIN CASSMAN, PH.D.

POSITION:
Acting Director, National Institute of General Medical Sciences (NIGMS), National Institutes of Health (NIH)

BIRTHPLACE and DATE:
Chicago, Illinois
April 4, 1936

EDUCATION:
B.A., University of Chicago, 1954
B.S., University of Chicago, 1957
M.S., University of Chicago, 1959
Ph.D., Albert Einstein Medical School, 1965

EXPERIENCE:
Acting Director, NIGMS, NIH, 1993-present
Deputy Director, NIGMS, NIH, 1989-present
Director, Biophysics and Physiological Sciences Program, NIGMS, NIH, 1985-1989
Senior Policy Analyst, Office of Science and Technology Policy, 1985-1986
Staff, House Subcommittee in Science and Technology Policy, 1982-1983
Chief, Molecular Basis of Disease Section, Cellular and Molecular Basis of Disease Program, NIGMS, NIH, 1978-1984
Health Scientist Administrator, Cellular and Molecular Basis of Disease Program, NIGMS, NIH, 1975-1978
Assistant Professor, University of California, Santa Barbara, 1967-1974
NIH Postdoctoral Fellow, University of California, Berkeley, 1965-1967
Research Fellow, Northwestern University Medical School, 1959-1961

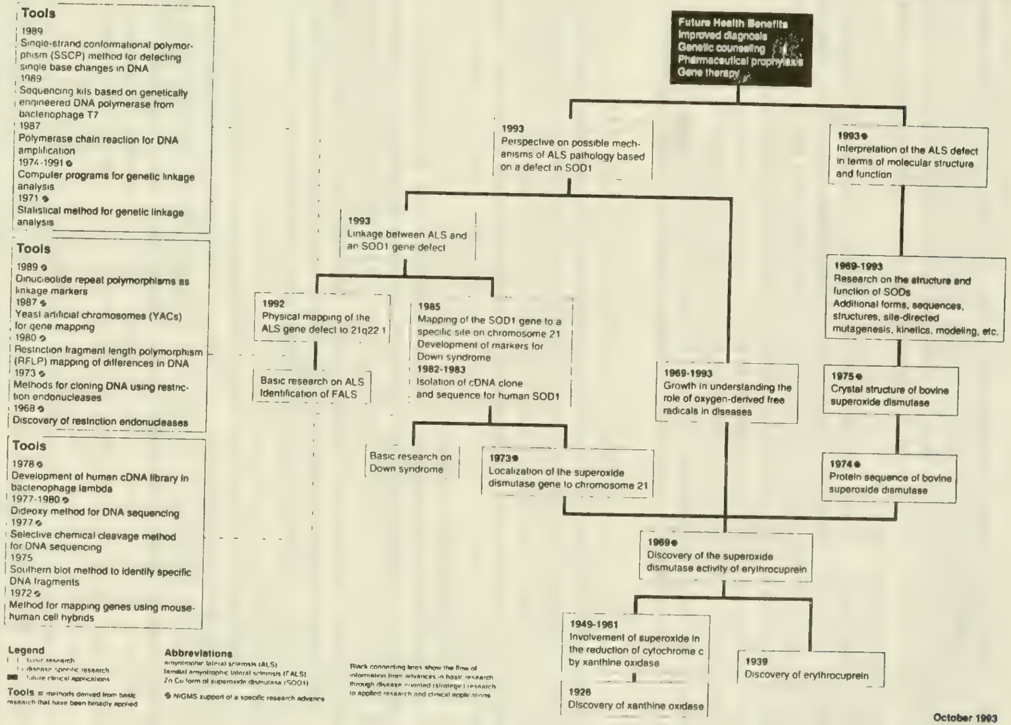
ASSOCIATION MEMBERSHIPS:
International AIDS Society
American Association for the Advancement of Science
Biophysical Society

SPECIAL AWARDS or CITATIONS:
Presidential Meritorious Executive Rank Award, 1991
Senior Executive Service Award, 1990
Senior Executive Service Award, 1989
Senior Executive Service Award, 1988
Senior Executive Service Award, 1987
NIH Director's Award, 1983
NIH Quality Increase Award, 1980

COMMITTEE MEMBERSHIPS:
NSTC Committee on Fundamental Science, 1994
PHS Human Radiation Studies Working Group, 1994
NIH Tuberculosis Executive Committee, 1993-present
NIH Task Force on the Commercialization of Intellectual Property Rights from NIH Funded Extramural Research, 1993-present
NIH Bioengineering Working Group, 1993-present
NIH Intramural Research Infrastructure Subcommittee, 1993-present
Chemical and Engineering News Advisory Board, 1993-present
NSF Advisory Committee for Biological Sciences, 1993-present
Chemical and Engineering News Advisory Board, 1993-present
NSF Advisory Committee for Biological Sciences, 1993-present
Shannon Awards Committee, 1991-1993
NIH AIDS Executive Committee, 1987-1993

Basic Research Contributions to Discovering the Molecular Basis of Lou Gehrig's Disease (ALS)

National Institute of General Medical Sciences



Tools
1989
Single-strand conformational polymorphism (SSCP) method for detecting single base changes in DNA
1989
Sequencing kits based on genetically engineered DNA polymerase from bacteriophage T7
1987
Polymerase chain reaction for DNA amplification
1974-1991 ◆
Computer programs for genetic linkage analysis
1971 ◆
Statistical method for genetic linkage analysis

Tools
1989 ◆
Dinucleotide repeat polymorphisms as linkage markers
1987 ◆
Yeast artificial chromosomes (YACs) for gene mapping
1980 ◆
Restriction fragment length polymorphism (RFLP) mapping of differences in DNA
1973 ◆
Methods for cloning DNA using restriction endonucleases
1968 ◆
Discovery of restriction endonucleases

Tools
1978 ◆
Development of human cDNA library in bacteriophage lambda
1977-1980 ◆
Dideoxy method for DNA sequencing
1977 ◆
Selective chemical cleavage method for DNA sequencing
1975
Southern blot method to identify specific DNA fragments
1972 ◆
Method for mapping genes using mouse-human cell hybrids

Future Health Benefits
Improved diagnosis
Genetic counseling
Pharmaceutical prophylaxis
Gene therapy

1993
Perspective on possible mechanisms of ALS pathology based on a defect in SOD1

1993 ◆
Interpretation of the ALS defect in terms of molecular structure and function

1993
Linkage between ALS and an SOD1 gene defect

1969-1993
Research on the structure and function of SODs
Additional forms, sequences, structures, site-directed mutagenesis, kinetics, modeling, etc.

1992
Physical mapping of the ALS gene defect to 21q22 1

1985
Mapping of the SOD1 gene to a specific site on chromosome 21
Development of markers for Down syndrome
1982-1983
Isolation of cDNA clone and sequence for human SOD1

Basic research on ALS
Identification of FALS

1969-1993
Growth in understanding the role of oxygen-derived free radicals in diseases

1975 ◆
Crystal structure of bovine superoxide dismutase

Basic research on Down syndrome

1973 ◆
Localization of the superoxide dismutase gene to chromosome 21

1974 ◆
Protein sequence of bovine superoxide dismutase

1969 ◆
Discovery of the superoxide dismutase activity of erythrocuprein

1949-1961
Involvement of superoxide in the reduction of cytochrome c by xanthine oxidase

1926
Discovery of xanthine oxidase

1939
Discovery of erythrocuprein

Legend
▭ basic research
▭ disease specific research
■ future clinical applications

Tools = methods derived from basic research that have been broadly applied

Abbreviations
amyotrophic lateral sclerosis (ALS)
familial amyotrophic lateral sclerosis (FALS)
Zn Cu form of superoxide dismutase (SOD1)

◆ NIGMS support of a specific research advance

Black connecting lines show the flow of information from advances in basic research through disease-oriented (strategic) research to applied research and clinical applications

October 1993

CURRENT AND OPTIMAL SUCCESS RATES

Mr. SMITH. I want to ask each one of you, first, the same question I asked yesterday: How many applications did you receive for grants? How many were awarded? How many do you think if you had the money really could very profitably have been awarded or should be awarded?

Dr. LENFANT. This current year, 1994, we expect to award approximately 700 new and competing applications. The success rate, that is what proportion of all the ones that we have received is approximately 26, 27 percent, which means that basically we will receive this year 2,500 applications.

The views of the Institutes and of our advisory councils and all of our advisory community have been consistently that we should support between 35 and 40 percent of all the applications that we are receiving.

Dr. GRADY. This current year we are funding 400 new and competing applications. Our success rate is 25 percent, which means that we receive approximately 1,600 applications in order to fund one out of four. Given the level of the science we would expect to be able to fund up to 40 percent of applications and still be funding outstanding science. That would bring the total to about 600 new and competing applications.

Dr. CASSMAN. In fiscal 1994, excluding our AIDS-related grants, we expect to award about 760 new and competing applications out of a pool of over 2,600. Our success rate will be somewhere in the region of 29 percent. And as with the other comments made, we would hope at some point to be able to go to 40 or even 45 percent. We feel the quality of the applications received are good enough to warrant that.

Mr. SMITH. Dr. Varmus, again I know you don't have the answer right now, but in each one of these Institutes, I would like to have some kind of indication as to what happens to the ones who did not succeed who really should have. What happens to them? Do they end up out of the loop? Or do they still do basic research in some other way? Send that to the Committee when it is available.

BASIC RESEARCH

We do basic research in this country, not only in the field of health but also technology. And we immediately make the results available. In the case of technology in the past too often people in other countries pick it up and apply it to something practical.

In your field, the basic knowledge, the results become available immediately, don't they?

Dr. VARMUS. Yes.

Mr. SMITH. And are the people in other countries picking it up and using it, too?

Dr. VARMUS. Yes, NIH is an international enterprise, and, yes, because the information is available, of course, we encourage it to be applied in other countries as well as our own. Many of the things that are done are done through international teams of scientists and it is not unusual for us to share scientific information.

Mr. SMITH. So in the case of the heart, we have put tens of billions of dollars into basic research in heart. I remember back when everyone gasped when they saw this first plastic heart that was going to be the answer to everything.

That was a good many years ago and there has been a lot of research done since then. As you indicated by your chart, the number of deaths in this country has come down substantially. Has the same thing happened in other countries?

Dr. LENFANT. Not in all countries. The United States and Australia, are the leading countries. The further east you go from the United States and from Western Europe, then the trend reverses. Clearly, the programs which are being conducted here have been extraordinarily successful and, again, the United States is leading the march in terms of decline of cardiovascular death rates.

Mr. SMITH. Well, this information is available to everybody. In some countries apparently—either the information has resulted in fewer deaths or else the change in lifestyle has, I don't know which.

LIFE STYLE CHANGES

Dr. LENFANT. I think that the issue, Mr. Chairman, in this country, the practicing community, and the public as well, are taking great advantage of the results of our research, and therefore modifying their lifestyle. And that is why we have such success in many ways.

Mr. SMITH. In other words, you think there has been a change in lifestyle and even if lifestyle is the major reason for the reduction in deaths, you attribute the change in lifestyle to the research that has been conducted.

Dr. LENFANT. Oh, absolutely. Absolutely. There is an awful lot of research that the Institute has supported in terms of how you should control your blood pressure or what dietary habits should you have, should you exercise and when and so forth. And the results from this research are passed on to the public as well as to the practicing physicians, as quickly as we can by way of educational programs that we sponsor.

Mr. SMITH. So the major objective is getting people to change lifestyle.

Dr. LENFANT. It is one. It is not the only one, but it is certainly one that is very important. That is something that each of us can do. There are a lot of things that we cannot do. We cannot modify our genetic determinant and the way that we are built, whether we are man or woman, we cannot change that, but all of us can influence the way we are conducting our own life.

Dr. VARMUS. This is related to a discussion we had with Mr. Hoyer about the nature of preventive medicine. Prevention obviously involves persuading the person at risk to adopt new behavioral styles, but that change is more likely to occur if it is based on sound scientific principles knowing that one has a certain genetic risk and knowing that certain diets change blood lipids and knowing that certain blood lipids predispose a person to heart disease. All of this is part of the method of persuading people to change their behaviors.

PROGRAM BALANCE

Mr. SMITH. That gets to the question of if we are spending $11.5 billion on the National Institutes of Health, are we spending the right proportions on the information to change people's lifestyles compared with the right proportions on basic research?

Dr. LENFANT. Well, I think it is a question which is very difficult to answer. I don't know whether it is the right proportion, but there is one thing that I know for sure, that is that the portfolio of basic research, which is supported by my colleague from the NIGMS as well as by our Institute and all of the Institutes, is really the key for us to provide true, valid information to the public. I think that when we talk in terms of prevention, the biggest mistake that one could make is to give the public faulty, wrong information. Thus, the basis of what we recommend to the public or with the patient is from the basic research which has been conducted.

So I just cannot make the statement that there is too much basic research. If anything, I would say perhaps not enough.

Mr. SMITH. No, I didn't mean there is too much basic research, but I wonder if there is enough packaging in an attractive form that people will watch this information and the results in order to convince people to change lifestyles.

Dr. LENFANT. I think that in the areas which relate to our Institute, we are just appropriate. We do what needs to be done.

KNOWLEDGE TRANSFER

Mr. SMITH. And then we have the intersection with new medicines. Some people think, well there is a new medicine; that is the solution. I can keep on in the same lifestyle. And then there is another problem, and that is even if it is four out of 1,000, as it was in one case that I know about, the new medicine caused another problem that was worse than the problem that he had.

The one case I am talking about that I know about, there was a new medicine for glaucoma, and after taking it several years they found out that was what was causing his asthma problems. In four out of 1,000 cases it caused that, but they didn't know it. His asthma was hurting him worse than his glaucoma. I just kind of wonder about whether or not our information is sufficient that flows out of all this new knowledge that we gain.

Dr. LENFANT. Well, I think that I am familiar with the example that you are citing here. It is true, indeed, that a handful of patients that received this medication developed some allergy but the fact is that hundreds of patients had considerable improvement in their glaucoma. So it is most unfortunate for these few patients and we learned from them, but many other individuals have greatly benefited from this medication.

PHYSICAN EDUCATION

Mr. SMITH. Well, I wonder, we are not talking about information for 250 million people. We are talking about the information for the doctors that prescribe the medicine. And you would have thought that maybe the information would have been used before the damage was done for several years. They didn't know this was one of the four out of 1,000. You get my point?

Dr. LENFANT. Yes, absolutely. Absolutely.

Mr. SMITH. I wonder if we are giving enough information to doctors to be alerted.

Dr. VARMUS. We give the information we have, Mr. Chairman. But obviously when one gives medications in many cases there will be unexpected side effects; and when those side effects are known, they are disseminated immediately to all prescribing physicians.

Mr. SMITH. Mr. Porter.

NHLBI'S BUDGET

Mr. PORTER. Thank you, Mr. Chairman. Dr. Lenfant, I have been somewhat mystified as to why your Institute has done so poorly in the last two budgets. Last year you were slated for a 1.3 percent cut and this year with some Institutes getting 5 percent increases, the NHLBI would get only a 3.7 percent increase. That is below the minimum 4.1 percent that Secretary Shalala identified as a minimum for NIH overall. In constant dollars your budget remains below the 1985 level.

This, to me, is an Institute that can show results. Stroke deaths have been cut by a third and despite the increase of the incidence of heart disease, mortality is declining. What are the consequences for research in the research community of funding your Institute at below inflation?

Dr. LENFANT. Well, this is a very complex question, which has, of course, many ramifications. You know, I could start by saying that I, like all of my colleagues at NIH, would certainly welcome having larger budgets, but at the same time, I do realize that the NIH is not alone and public health in this country is faced with enormous problems and some hard decisions have to be made which may increase a budget more than another one.

One thing that I mentioned earlier is that although our Institute is heart, lung and blood, there is no question that in a way we do benefit a great deal from research which may be conducted in other areas. Take the example of AIDS research. Lots of things have been learned through this research effort, and our Institute has benefited from this research in several of our areas of interest.

Your question is what impact does it have? The impact is that research that we are doing, and I hope successfully, is going to be conducted and completed in a period of time which may be longer than if we had more funds, but they will be done eventually because we know where we are going.

Mr. PORTER. I am concerned that the figure is below inflation. That means that you are going in reverse, essentially going down, instead of up.

Dr. LENFANT. That is correct.

HEALTH CARE SAVINGS

Mr. PORTER. That concerns me. Dr. Lenfant, I have been trying to impress on everyone the great contribution that biomedical research makes to reducing the costs of health care. The NIH savings book lists a trial you supported on cardiac arrhythmia suppression which found that physicians were treating mild cases with unnecessary diagnostic procedures and drugs.

When physicians adopt these findings in their practice of medicine, we will save over $100 million annually by eliminating unnecessary treatments. I wonder if you could comment on that.

Dr. LENFANT. Yes, the case that you mention is indeed a very interesting one. The specific result from this study has not been to save so much money, but to save lives. We kept people from being hurt by the prescription which was commonly given. To the extent that I can make a generic comment let me say that it is extraordinarily important to conduct clinical studies, clinical trials, to validate new interventions such as devices like the artificial heart that was mentioned earlier, or drugs. Our Institute is doing a lot of that. If we were to sum up the savings which have resulted from the clear demonstration of the efficacy of a number of interventions it would be quite a sum of money.

RESEARCH TRAINING

Mr. PORTER. This is where real savings can be made in terms of health care treatment, and I believe the White House has to pay a great deal more attention to biomedical research. Your Institute shouldn't be going down. It has got too great a role to play.

Last year and yesterday I asked Institute directors about the impact of underfunding on the flow of new scientists into research. Virtually every director told us that new scientists were discouraged if they are underfunded. They are choosing other careers and we are at risk of losing an entire generation of scientists.

As we look at NIH numbers, we see that training has declined by 25 percent over the last decade as a percentage of NIH's budget. Training slots at NHLBI have declined from 1,709 to 1,590 during that time. Why has NIH dedicated fewer of its available resources to training, and what is the impact of funding fewer total training slots at your Institute?

Dr. LENFANT. Well, the first question is why is NIH doing so. I think it is in response to a budgetary constraint which affects everybody at NIH. Our problem is not unique. What is the impact of this problem? As we bring fewer individuals into our research enterprise the impact of that is going to be that less will be done within a given period of time. And it is true that we are witnessing a downward trend which is very difficult to control.

There is no question but that physicians now that are attracted to go into the practice of medicine, which is certainly a much more lucrative career, do impact on our program in a somewhat negative way. As long as the stipend and the salaries for young people coming up into the system will be what they are, there will be a very difficult career decision to be made by this individual.

I don't want to end on a negative note. I would say because that there is so much going on in our Institute we keep on attracting a number of very, very good people, but not as many as we would like.

SUCCESS RATES

Mr. PORTER. The NHLBI estimates a grant success rate of 27 percent for 1994. The budget estimates a rate of 30 percent for 1995. That is high among the Institutes, but below the 40 percent that Dr. Varmus and Dr. Burgess suggested that we should aim for and below the rate you had in 1986. What are the implications of long-term depressed award rates?

Dr. LENFANT. Well, it is just what I was saying; that neither the needs that we have and the opportunities which are available to us are going to be fully pursued. The problem that we have is a problem that is common to all of the Institutes. And I suspect the impact is going to be the same for all the Institutes.

Mr. PORTER. We sit here and listen to the testimony on all the different departments and all the different programs at the Institutes and all the rest, and collectively must somehow come to conclusions as to what is the highest priority for which we should be spending money.

Inevitably, with downward pressure on the budgets that puts different priorities in conflict with one another and we have to choose among them. And while I realize that all of you have to be good team players with an administration budget that you are here to defend, we also have to understand how important what you do is compared to what others do, and how losing momentum or losing researchers or losing the opportunity to save money on health care treatment, prevention, is important. And that is why I am asking these questions because I think it is a tremendous issue. NIH is the most important thing we look at.

Others may differ on this. And that is why I ask these questions. I realize it puts you in a conflict with your own administration, and you want to be loyal players in that regard. But we have to know what really is important and why we should fund your Institute or the NIH at a higher priority than other competing priorities. That is why I ask it.

NATIONAL CENTER FOR SLEEP DISORDERS RESEARCH

Let me ask this question: What progress have you made in establishing the administrative structure and program activity for the National Center for Sleep Disorders Research?

Dr. LENFANT. Well, we have done comparatively well, considering. I am pleased to tell you that earlier this week, the document which formally established the Center has moved out of the Public Health Service to the Secretary's office. So I expect a final signature to be obtained very soon.

However, the delay in formally establishing the Center has not detracted us from moving forward with other important issues. For example, we have developed space within our Institute to house the Center. We have made a couple of appointments, but not that of the director, this is being held up for a number of reasons. We have—Dr. Varmus actually has appointed the members of the advisory committees which are to develop the research plan for the Institute and for the NIH as a whole. Finally we have issued a solicitation for some new programs. So things have been moving.

Again, I am personally a little bit disappointed and frustrated that some administrative steps haven't been fully completed, but as yet the program has not suffered from that.

Mr. PORTER. Last year you listed the National Sleep Awareness Campaign, a public education initiative, as one of the top priorities for the Center. I believe this is perhaps the most important activity the Center can undertake, and I wonder what the status is of this education initiative.

Dr. LENFANT. The meetings which are necessary to bring all the interested parties to work with us to develop this campaign are being scheduled now. I think I can safely say that—by the end of summer, we will have a plan in place to initiate this campaign and the campaign will have started.

I should tell you that we are at this time already working with the Department of Transportation.

Mr. PORTER. One final question, if I may, for you and then I must reserve my questions for Dr. Grady and Dr. Cassman. In response to this subcommittee, NIH undertook a financial management planning process four years ago. The NHLBI had an innovative approach to the problem of containing costs.

What was your approach and what effect has it had?

Dr. LENFANT. Well, we have done a great number of things which I would be pleased to describe at some length for the record if you wish, but I can give you the bottom line, which is that in 1990, fiscal year 1990, the National Heart, Lung, and Blood Institute, was funding only 28 percent of our new and competing grants at full cost, that is the cost recommended by the study section.

Today or last year in 1993, which was the last year that we have complete data, 68 percent of our grants were funded at full cost. My expectation is that this year this number will be between 75 and 80 percent. And my expectation is that by 1995 we may reach 90 percent of our grants competing and new grants to be funded at full cost, that is cost recommended by the study section.

Mr. PORTER. That is why your budget is not going up as rapidly. You are too efficient.

Dr. LENFANT. I don't know about that.

Mr. PORTER. Thank you.

MINORITY HEALTH DISPARITIES

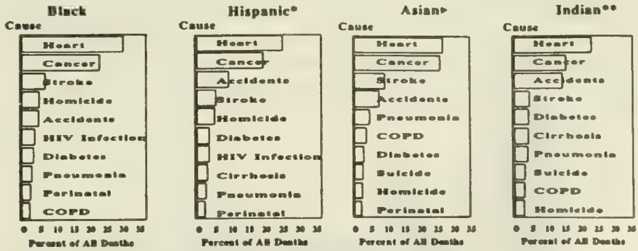
Mr. SMITH. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman. I have questions for all three of the directors, but let me start with Dr. Lenfant. Dr. Lenfant, I have a document here which contains information from the National Heart, Lung and Blood Institute's fact books. It shows 10 leading causes of death among minority groups in total, and then under each category, Black, Hispanic, Asian and Indian, it lists the 10 leading causes of death.

[The information follows:]

10 Leading Causes of Death Among Minority Groups

United States: 1990 & 1991



Note: Data are for 1990 (Asian, Indian) and 1991 (Black, Hispanic).

* Data for 47 reporting states and the District of Columbia.

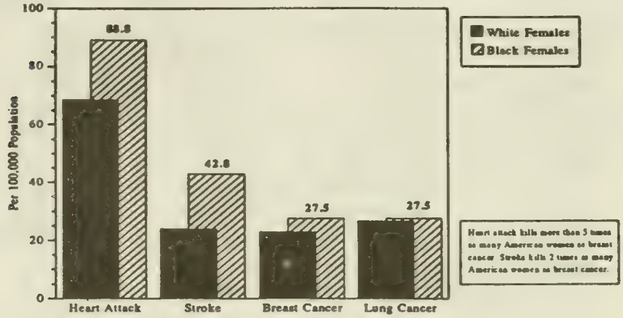
▸ Includes deaths among individuals of Asian extraction and Asian-Pacific Islanders.

** Includes deaths among Aleuts and Eskimos.

Source: Vital statistics of the National Center for Health Statistics
National Heart, Lung, and Blood Institute Fact Book, Fiscal Year 1993

Heart Attack and Stroke vs. Breast and Lung Cancer In White and Black Females (Age-Adjusted Death Rates)

United States: 1990 Final Mortality



Heart attack kills more than 5 times as many American women as breast cancer. Stroke kills 2 times as many American women as breast cancer.

Source: National Center for Health Statistics and the American Heart Association

Mr. STOKES. It is interesting that they are almost identical. However, there are some differences. For instance, for blacks, the first leading causes of death are heart disease, cancer, stroke, homicide, and accidents. For Hispanics, they are heart disease, cancer, accidents, stroke, then homicide. For Asians, they are heart disease, cancer, stroke, accidents, and pneumonia and five others. For Indians, they are heart disease, cancer, accidents, stroke, and diabetes.

Tell us, are we making any progress at all in terms of reducing the disparity between health care for the majority population and the minority population?

Dr. LENFANT. The answer to this question is an unqualified, yes. The issue is are we doing as well as we could or should? The answer to that is probably, no.

And so the next question is why is it so? I don't know that I have an answer. I think that there are many, many research questions which need to be addressed and investigated.

Mr. Stokes, you know you ask me this question each year that I come here.

Mr. STOKES. Yes, for many years, we have been going through this. And, I can't say that we have gotten the right answer yet.

Dr. LENFANT. Yes, each year I give you the same answer. We are making progress, but the decline of coronary heart disease is not as fast for minorities, particularly for African-Americans, as it is in Caucasians.

Why is it so? I don't know. I mean, there are lots of factors, but which ones should be addressed first? I don't know.

One thing that we have done this year because of our concern, not exactly to know which direction we should take is to convene a number of experts to help us to develop a plan. In fact, here is the plan in question that I would be glad to give you a copy of. It is titled "Research in Coronary Heart Disease in Blacks." And this document, I think, gives us some directions, initiatives that can be taken.

I hope that by implementing some of the things which are in this document, we will be able in the near future to give you a much more positive answer to your question.

Mr. STOKES. The bottom line, Dr. Lenfant, is that you are saying that we are still studying the problem?

Dr. LENFANT. That is correct. You know, Mr. Stokes, the budget which is allocated to minority health and related issues, is 12 percent of our total budget. And we keep on increasing it each year. We are making progress. But I have to say to you not as fast as we want.

NATIONAL MARROW DONOR PROGRAM

Mr. STOKES. Let me ask you about another area, Dr. Lenfant. with respect to organ tissue and marrow transplantation, what is your Institute doing to improve the chances of patients from underrepresented groups in finding matches.

Dr. LENFANT. Yes, the Institute has set aside some money which has been awarded to organizations in localities where there is a large minority population, and we are indeed making progress. Today the rate of recruitment of minorities is about 20 times what it was two or three years ago. The number of transplants in minorities is also increasing a great deal. However, Mr. Stokes, I have to to tell you that there is a problem that you and I can do nothing about it.

You see, it is much more difficult to find a match for some minorities than it is for nonminorities. You understand what I am saying?

Mr. STOKES. Yes, I do.

Dr. LENFANT. For some nonminorities the probability to find a match today is about between 60 and 70 percent. The probability to find a match within the same number of donors for minorities would be only between 30 and 40 percent. The reason is that the phenotypes are more numerous in minorities than they are in nonminorities. This problem is a very significant one.

STROKE RESEARCH

Mr. STOKES. Thank you. I will have a number of other questions for you after, but for now, let me direct some to Dr. Grady of the National Institute of Neurological Disorders and Stroke.

Dr. Grady, stroke is America's third leading cause of death, the leading cause of serious disability and a major contributor to late life dementia. The news media right now is projecting the fact that a former President of the United States has just had a very serious stroke.

Can you tell us, first, how much stroke research will the President's budget allow the Institute to support in fiscal year 1995?

Dr. GRADY. We estimate being able to spend approximately $73 million in the area of stroke in the coming year based on what we know in the President's budget. You are correct, Mr. Stokes, it is the third leading cause of death. We have made enormous progress in this area, but we still have a long way to go.

One thing which I would like to bring to your attention, since you mentioned the former President. One of the things that we have seen in the area that has changed enormously in the area of stroke is that stroke is now considered an acute disorder. The situation used to be that if you got a stroke, you had it and that was it. Now, and this is borne out by the newspaper stories, people are brought immediately to medical centers where treatment is available.

We do not have all the answers yet, but we do have experimental drugs for treatment including anticoagulants to break up the clots that are blocking vessels and there are drugs under investigation to save brain cells that will be used immediately after the blood flow is restored to an area. The idea is that those cells surrounding the actual area of damage in the brain are still viable, they are alive but not well, and if you get the right drugs to the area you can potentially decrease the amount of damage that occurs with a stroke.

We, together with voluntary agencies last year, developed guidelines for the emergency treatment of stroke within the first six hours. The newspaper accounts, in fact, detail that the former President was taken to New York City by plane within two hours, which is what we are aiming for in the early treatment of stroke. We have been able, we think, to extend that time window some, and that is still being tested by other approaches.

Mr. STOKES. Does swelling of the brain from stroke create a very special problem?

Dr. GRADY. It does in some circumstances. That depends on the extent and type of the stroke. If there is a very large area of damage, then the swelling tends to be greater, and it also varies for certain types of stroke. Blocking of blood vessels tends to be associated with less swelling than bleeding into the brain because there is also more space being occupied by the blood clot. So, again, it can be a serious problem. And it is one of the very important reasons why it is essential to get patients affected with stroke into the hospital as quickly as possible.

Mr. STOKES. It is my understanding that African-Americans, have a more than 60 percent greater risk of death and disability from stroke than white Americans. Is that an accurate figure? And if so, can you tell us why the risk is greater?

Dr. GRADY. The actual figure depends on the type of stroke, but you are correct, Mr. Stokes, that the percent of stroke or the chance of stroke is greater in African-Americans than non African-Americans. It is also higher in male African-Americans than females. We have several studies currently underway to try to determine the exact incidence of stroke in minorities, African-Americans, and Hispanics, as compared to the nonminority population. But we are also looking at the type of stroke that affects these populations as well as the risk factors.

For example, we do know that diabetes is a risk factor which increases the chance of stroke in African-Americans and particularly in Hispanic populations. There are three studies going on in New York City at this time addressing these issues that I have just described.

We have also just begun another study in the area of Cincinnati looking at hemorrhagic stroke, the type of stroke that does affect the African-American population in higher incidence. That is a population-based study to look at all the individuals in that area to determine the incidence and the subtype of stroke and the risk factors.

I would like to pick up on something that was mentioned earlier by the Chairman, the idea of being able to change lifestyles.

One of the things that we have found—and we have actually learned a lot from our colleagues in the Heart Institute who have been at this business a little longer in the early days than we have—but we have learned that there are a number of risk factors that can be modified, but there are some that can't. The single greatest risk factor for developing stroke is age. Coming along after that you have smoking, which we can do something about, hypertension, diabetes and others.

As for dietary modifications, to some extent that is useful in many patients, but to some extent it is not. However, having identified your at-risk population and having done what one can in terms of changing lifestyles, then one can look at alternative methods such as cholesterol-lowering drugs. That is really what we are looking at: identifying the specific stroke subtype and being able to develop rational interventions for the populations as appropriate to those populations.

Mr. STOKES [presiding]. Thank you Mr. Chairman. Doctor, my time has expired. Mr. Bonilla, I yield to you.

ALLOCATING RESOURCES

Mr. BONILLA. First of all, I would like to, associate myself with the concerns that Mr. Stokes has expressed about these medical problems that affect disproportionately minority populations and specifically in south Texas where I have an area that is over 60 percent Hispanic. My first question is a general one and it is something that concerns me.

There is not a member of this committee that is not concerned about funding every area of medical research, including myself. There is a concern that I have that sometimes what may be perceived as politically correct supersedes what is medically correct. Specifically, we have, as Congressman Porter pointed out, an effectively reduced budget when you factor in inflation for all three Institutes represented here today.

INCREASED FUNDING FOR AIDS

And over the last five years, for example, we have seen to correct discrepancies in the past with increased funding in the area of AIDS, for example. And while acknowledging that that has been a discrepancy we have now, I feel, treated the discrepancy among other areas of research that the politically correct may not understand that they are politically incorrect for overlooking areas of research that affect minority groups.

So my question, I guess, for each of you here today, the three of you who have testified is: Are you concerned that this is factored in and may have superseded in some cases what is medically correct?

Dr. GRADY. Would you like me to start?

Mr. BONILLA. That is fine, Dr. Grady or Dr. Lenfant.

Dr. LENFANT. This is really a very difficult question. And I frankly don't know how I can come up with a satisfactory answer because there are so many elements which should be considered in providing an answer. Areas of research to which large and seemingly disproportionate resources are allocated such as AIDS, for example, represent an enormous problem, not only in the United States, but worldwide.

Having said that, it is also certain that cardiovascular disease and stroke are enormous public health problems particularly for minority citizens. Unquestionably, there are many opportunities to do more than what we are doing. However, the decision of how funds are distributed is not one which is within my purview and I would like to leave it at that.

Mr. BONILLA. Dr. Grady.

Dr. GRADY. We obviously share your concern in a very large fashion, Mr. Bonilla. Having the responsibility for addressing over 600 neurological disorders, it is very difficult to give the amount of attention to every single one that we might like to at different times. We are at a very, very difficult and exciting time in neurological sciences, as I said earlier in my opening statement.

For many years, we could do very little except say this is your problem and we can't do anything about it. Right now, we are at a crossroads. Because of a lot of investment in basic research, we are finding out what causes many of these disorders and we can actually begin to approach intervention and being able to if not cure or prevent the disorder, to be able to stop it in its tracks or slow it down.

Although neurological disorders do affect the very young and also the very old, the majority of the population that they affect are middle-aged people who then go on to live nearly normal life spans. But they live them with an increased and increasing disability as time goes on, with less ability to care for themselves and more need for support from the health care system.

So we would make the case that a very early investment in these areas is not only good for the patient population, but also cost-effective for the country.

I have to agree with Dr. Lenfant, we all have our priorities and it is hard for me to argue that ours are more urgent than anyone else's, but because I deal with them on a daily basis, I know that they are extremely urgent.

Mr. BONILLA. Not only urgent but affect a great, great, massive part of the population.

Dr. GRADY. A very large part of the population, yes, and that also is something that we really need to keep in mind. Again, we will do what we can. I think you know, this is a very critical time in the field and we will do as much as we can as fast as we can.

The concern is that all these opportunities are available, but that the opportunities will not be available forever, and so we really want to get in and do what we can while we can.

AIDS RESEARCH

Dr. CASSMAN. Let me speak directly to the issue of the AIDS funding. In our case, in fact the funds we received allowed us to establish a program that I don't think we could have done otherwise and I think in fact was very innovative. It was a program designed to develop the concept of structure-based drug design. This was about eight years ago, and this approach to drug design is not nearly as unusual now as it was then. But it was still speculative, highly so.

And we were able to initiate this program because the funds were not targeted so narrowly that we were forced to put moneys into areas that might have been less scientifically productive. In fact, I think the research that has come out of the areas that have been supported by these AIDS dollars have had very broad benefits because, although they were targeted specifically toward AIDS systems, the methodologies and concepts that were generated through this funding are of value to an enormous number of potential outcomes. And in fact, the biotechnology industry now has something like 6 small start-up companies that are devoted exclusively to using structure-based drug design.

Now, we didn't contribute to all of that industrial application, but we certainly had an input into it. So the Institute really had the opportunity to use these funds for fundamental research that was related to AIDS but not targeted so narrowly that we couldn't use our judgment in deciding where the appropriate input would be.

Mr. BONILLA. Just so you all understand, I am a new Member, as you know, of Congress and coincidentally, just because I happen to live near people and associate with physicians who are teaching doctors back in Texas, before I even thought about coming up here, they would often express to me the concern that I am expressing to you today.

They are not obviously part of NIH but they receive NIH funds and have received NIH funding over the years, and that was something that was expressed to me very strongly by several doctors that I had just coincidentally befriended over the years, even before I thought I would be running for this office, so it is why I bring it up.

I have got to yield—well, they are all voting and I have to get over to the Floor and vote. We can continue, and if another Member comes back then I can continue on the next round. Thank you.

[Recess.]

UNSUCCESSFUL APPLICANTS

Mr. SMITH. Dr. Varmus, while we are waiting, I am somewhat puzzled and maybe you can't answer this right now, but let's put the whole thing together. We have this question of how much to spend for each one of these Institutes which involves how many grants we should have in each Institute, but it doesn't stop there. We need to know, then, what happens to the ones that are not approved. If some of them are the source for some private foundations acquiring investigators, it is not all lost.

I don't know if it is or not or to what extent it is.

Dr. VARMUS. Well, Mr. Chairman, there are very few voluntary organizations who actually hire investigators. The only example I know that has a major impact on what we do is the Howard Hughes Medical Institute. Those investigators who work for the Howard Hughes Medical Institute, in general, have a very high success rate.

Mr. SMITH. Well, I wasn't stopping there or if drug companies use these as sources for people they need for trials.

What is the right amount of resources to devote to NIH and to each one of these Institutes? We haven't really done a very good study of that, have we?

Dr. VARMUS. Well, you are raising a couple of issues that are probably separable and in many ways connected. First in the utilization of manpower, and second is how much energy and money should go into the pursuit of biomedical research at this particular time regardless of how much manpower has been developed. Those are related issues and there have been studies of some of these questions in the past.

I think the question you are raising about the fate of individuals who have not succeeded in being awarded a research project grant is an interesting one that I have been quite concerned about myself and maybe your questions stimulate support to alleviate this problem.

Mr. SMITH. We really need answers to that, don't we?

Dr. VARMUS. That is an easier one to address than the question of what is the proper level of funding for the whole biomedical research endeavor. The former issue is one where guidelines for alternate solutions can be established. It is very difficult to come to a simple conclusion.

HEART DISEASE IN OTHER COUNTRIES

Mr. SMITH. Then we come to this interesting graph you have about deaths in the United States from heart problems. They have been reduced in the United States more than any other country, but the medical research is available to all countries. So it isn't just because we had an edge on research and technology; there must be some other reasons.

I just doubt very greatly that life-style changed that much in the United States compared to other countries. In fact, it looks to me like life-styles are getting worse in some respects instead of better. I don't think we improved our life-style enough to make a reduction in the number of deaths from heart problems.

Why didn't deaths decrease in France at this rate?

Dr. LENFANT. They are, but not as much. It may very well be that the approach to the treatment of these conditions may be different but, for example, if you take a place where it increases, in Eastern Europe, we know what the issue is. The issue is that there is neither coronary bypass or angioplasty and very few have access to it.

In fact, I do remember when a few years ago I was in the northern part of the Soviet Union and the people were going to Scandinavia to get treatment of their coronary heart disease.

Mr. SMITH. Let's compare United States to Saudi Arabia. What is the death rate?

Dr. LENFANT. In Saudi Arabia, the rate of coronary heart disease is increasing because of the so-called "westernization" of Saudi Arabia. This is a very interesting phenomenon that we have seen for the last 50 years, namely that in countries where you have a decline of rheumatic heart fever, which is a very prevalent disease in this part of the world——

LIFE STYLE FACTORS

Mr. SMITH. So now we are back to life-style because there isn't any shortage of medical facilities available in Saudi Arabia.

Dr. LENFANT. That is correct.

Mr. SMITH. For instance, they have furnished everybody whatever they want for free. The hire doctors from all over the world, build the hospitals, so there isn't any shortage there.

Dr. LENFANT. Life-style works both ways. It can help you but it can also hurt you, and this is what you see in some parts of the world—in the Middle East in Saudi Arabia, For example, everybody smokes and the diet is not really——

Mr. SMITH. That is what I say, we are back now to life-style, aren't we? It can't be just that they didn't have the medical facilities available like in Eastern Europe. It is because the life-styles are changing. Life-style is very important, isn't it?

Dr. LENFANT. It is when it comes to conditions like high blood pressure, for example. Today, in the Arab countries, the prevalence of high blood pressure is even higher than it is in the United States. And in the United States, it is a terrible problem which in fact is related to the stroke issue that was discussed earlier.

If you could do away with high blood pressure in the United States, there would be fewer strokes.

HEALTH CARE AND PREVENTION

Mr. SMITH. Well, it is kind of puzzling when we start looking—everybody is talking about health care now. This is the big question, you know. And I just wonder if we really are doing enough studying about the relationship of one thing to another and what part it plays in the whole scheme of things including stress, including life-styles, and the whole thing.

I just wonder if we are fitting the whole thing together and looking at the total resources we are going to spend and trying to allocate them, including information about what we already know.

Dr. GRADY. If I might address that, Mr. Chairman.

In the neurological disorders I spoke about earlier, there are a number of disorders that we cover, over 600, and many of these are rare disorders, many of them are prevalent, and we do not have cures or treatments for many of them.

But because of all of the work that has been going on, we are getting a handle on a number of them and by doing that, I think one of the answers to your questions is that the whole health care system can be greatly improved, at least in the area of neurological disorders, by the research that tells us how to prevent these disorders, how to treat or at least how to slow them down.

There are a number of examples of this. We talked about stroke earlier, and I won't go over that again. But also, for example, young children are prone to have high fevers and they may have seizures during that period of time. In febrile seizures, a study that we completed last year that was funded by NINDS showed that the administration of the drug valium, given during the early period of time of the febrile seizures will prevent the post-febrile seizure episodes from recurring into full-blown seizures for the lifetime of that child. Without treatment, 50 percent of these children would go on to have a history of seizures throughout their lifetime.

Providing this early treatment prevents the greater part of that population at risk from developing life long seizures. So, again, this is an improvement in quality of life, and it has a major impact on the health care system. The earlier example I used of indomethacin in low birth weight babies shows that if you can prevent an illness of a child, you prevent it for the lifetime of a child and in all of those who have a similar risk of disability.

The low birth weight infants are very prone to bleeding inside of their brains and use of this drug prevents that in the largest percentage of those treated. It was a very dramatic finding because those babies, if they do bleed in their brains, are prone to cerebral palsy and other developmental disorders as well as subtle cognitive deficits that will impair their being able to learn and become productive members of our society. These are very inexpensive treatments that provide a major benefit.

Mr. Bonilla has just left and had asked about strokes. In the area of San Antonio, we fund an ongoing study in the area of strokes which has just shown us that the use of aspirin will prevent about 80 percent of strokes in patients with atrial fibrillation. And the use of aspirin is interesting because the choice was aspirin or anticoagulation medicine. To prevent strokes people under 75 with atrail fibrillation who have no additional serious risk factors can take aspirin, a relatively cheap drug as opposed to anticoagulants which are more expensive and dangerous.

Not only that, but anticoagulents are associated with side-effects that require patients to come in and access the health care system repeatedly for blood tests to see how their clotting system is working and to make sure they are not having side-effects.

These are examples of research studies supported by the Federal Government that can in fact impact in a very importent way on the health of the American people and the access required of the health care system.

Mr. SMITH. Well, of course, there is nothing new about knowing that aspirin thins the blood. That was known by my father who had three years of medical school. He was to take four and they closed the school. He never got the fourth year. He was nevertheless the doctor in underserved areas and he prescribed medicine, aspirin, for people that had high blood pressure years ago. It's fine as long as you don't take too much and get the blood too thin.

Dr. GRADY. We would have liked to have him on our team because he was what we call an intuitive investigator. What we are trying to determine now is to make sure that we aren't using aspirin for people that it would not help and, therefore, could be hurt if they required a stronger drug.

MINORITY HEALTH DISPARITIES

Mr. SMITH. It is interesting this morning you discussed with Mr. Stokes, as I understood it, that the death rate is not being reduced in minorities as much as in the white population.

Dr. LENFANT. That is correct.

Mr. SMITH. Does that mean that the life-styles are not changing as fast there?

Dr. LENFANT. That is correct, too. It is a very interesting phenomenon that some 30 years ago, we were all talking about the "epidemic" of coronary heart disease. Lots of people were dying from it. However, much progress has occurred and we now witness the decline that you saw on the chart.

There are still a great number of people who are dying from coronary heart disease but they are dying in the later part of their life, 60s, 70s, 80s.

With African-Americans, we haven't shifted the age at which they die. Many minorities die at an earlier age than white.

Mr. SMITH. If they are not changing their life-style as fast as others in the same country and the same society, we ought to be asking why that is?

Dr. LENFANT. It can be life-style, it can also be access to care.

MINORITY ACCESS TO HEALTH INFORMATION

Mr. SMITH. And maybe access to information that is packaged in such a way that it influences them.

Dr. LENFANT. Well, it may also be access to information. There is another element that we haven't discussed today. We have some very strong data showing that stress and behavioral factors affect the conditions that I am talking about, coronary heart disease, cerebrovascular heart disease, hypertension.

There is no question that minorities, particularly African-Americans, number one, have more stress and do not respond to stress in the same way as other people. These are very, very complex issues.

The bottom line is that, indeed, for the Caucasian in the United States the death rate decline is approximately four percent per year. For blacks, it is approximately 2.6 percent per year. So this is a big disparity. And to find a solution to this problem is very, very, difficult. But I think that now we are beginning to know what needs to be done.

Mr. SMITH. In a year and a time when we are talking about communication superhighways and all that, it seems like we are not putting enough resources into communications.

PUBLIC EDUCATION PROGRAMS

Dr. LENFANT. Well, communication and education are, of course, very important. I really would like to pursue a little bit the concept that Dr. Grady was mentioning. We come here and we talk to you about some aspects of our research programs but, in fact when you look at what we do, you see that there is a spectrum of research that clearly goes from the most fundamental research, at the cellular or even subcellular level to research on educating the public. All the steps in between these extremes are part of a research continuum which, in my opinion, is absolutely necessary to make progress.

Mr. SMITH. I think we are finally learning a lot from children. We find that you can do an awful lot with children. They can do a lot for themselves if you package educational material in the right way so that they will watch it. They can learn more by themselves watching a few of these programs than a teacher can teach standing in front of them for a lot longer time. Maybe we are not packaging the information we have so that people will get it.

Dr. LENFANT. Well, this is happening, Mr. Chairman. Now we have very clear evidence that, cardiovascular disease, cerebrovascular disease, arteriosclerosis, hypertension are beginning to develop during the teens. Therefore, this is why it is so important to have intervention at a young age to prevent the occurrence of these diseases.

Our Institute has many programs where we do that and they are very successful. There is one in New Orleans which has been going on for 20 years and another one in Iowa where children have been educated about prevention given and subjected to a more healthy diet than elsewhere; these studies demonstrate very clearly the benefits that can result from early education and intervention in children; as Dr. Grady was mentioning.

Mr. SMITH. I have to go vote.

[Recess.]

MINORITY PROGRAM FUNDING

Mr. STOKES [presiding]. Dr. Cassman, let me start with you. Please explain the proposed funding for the programs of your Institute that are aimed at increasing the participation of underrepresented minorities in biomedical research. Also, point out for us how the levels of funding compare to the 1994 levels.

Dr. CASSMAN. Let me say, first of all, as a blanket statement, that all of our minority programs, the training and research programs are going up by 6 percent. This is even in the areas such as training where the training line overall is flat; so we have moved money around within that line to assure that the minority programs get a significant increase.

And that is an increase that is noticeably larger than for any other parts of our programs. Our regular research grant programs will be increasing by 4 percent, so we have made a real effort to ensure that the minority programs maintain a reasonable rate of growth.

The proposed budget numbers are: for the Minority Biomedical Research Support program, MBRS, roughly $36 million; for the Minority Access to Research Careers program, MARC, about $15.7 million. The national pre-doctoral fellowships which were initiated in 1991 received a very substantial increase this fiscal year, in 1994. They will be getting again a 6 percent increase in 1995, going up to 151 trainees for about $3.5 million.

The total, including research supplements, pre-doctoral fellowships and some funds for proposed new initiatives that Dr. Poodry might be interested in establishing, all amount to $61.8 million. Of course we also have a substantial amount of co-funding from other Institutes. About 14 of the other Institutes contribute to the MBRS program. There is some contribution to MARC and we have gotten in particular a significant amount from Dr. Ruffin's Office of Research on Minority Health, in a number of different areas, but particularly in the Bridges program which was established just two years ago to stimulate the transition of students from the two-year to the four-year colleges and from the master's to the Ph.D. level. When you count them all in, including the co-funding, it amounts to almost $90 million.

PARTICIPATION BY HBCUS

Mr. STOKES. As you know, 20 years ago, when the MBRS and the MARC programs and so forth were established, there was a high concentration of minority students attending the Historically Black Colleges and Universities. With more and more minority students being admitted to the majority institutions, there has been perhaps some deemphasis in terms of seeing that students attending Historically Black Colleges and Universities are also participating in these biomedical programs.

What is that situation today?

Dr. CASSMAN. Well, they still have a major role. Let me talk about the two primary programs of MBRS and MARC. Of the 98 institutions that we are currently funding in MBRS, 51, over half, are HBCUs. For the MARC program, I believe the number is 69 institutions and over half—36—are HBCUs. There are obviously other institutions that have moved into the picture, as you say, as the demographics have changed. However, HBCUs still maintain a very significant role in these programs.

Mr. STOKES. Does this apply also to the Bridges programs?

Dr. CASSMAN. For the Bridges programs, the largest number are for the transition from two-year to four-year institutions. A number of two-year institutions are certainly strongly minority. I don't believe they would be classified as HBCUs, but certainly the opportunities are there. However, 5 HBCUs are participating in the Bridges program.

MARC EVALUATION

Mr. STOKES. I am going to have several other questions along that line which I am going to put in the record. However, let me also ask you, what is the status of the evaluation of the MARC Honors Undergraduate Research Training Program.

Dr. CASSMAN. It is well under way. A sample questionnaire has been developed and tested at one institution. The evaluation contractors are beginning their site visits. I think they have already conducted one, and they are going to do another. We expect to have a report available in a year to 18 months, but no longer than that, sir.

PRIORITIES OF MORE PROGRAM DIRECTOR

Mr. STOKES. You told us in your opening statement that you have just appointed a Director of Minority Opportunities in the Research Programs Branch. What are the top priorities of the new director for this very important effort?

Dr. CASSMAN. He is going to be very busy. We are looking at all of our minority programs in the same way that we are reexamining our programs in the rest of the Institute. As you know, the MARC and the MBRS programs are very long-standing. We now have added a variety of additional programs. Among them are the national pre-doctoral fellowships which can go to any minority student, whether he or she comes from an undergraduate experience at an HBCU or elsewhere, or from a MARC program or elsewhere, as well as the research supplements and the Bridges program. We need to make sure that all of these efforts are coordinated properly. I think that is really the highest priority, to make sure that there is no duplication, that the emphases are appropriate for the programs, that we still have the appropriate eligibility and merit criteria that we are asking of the participating institutions and students. It is more a matter of coordinating and integrating what we have and then seeing what we need and trying to fill those holes.

GENE THERAPY FOR SICKLE CELL DISEASE

Mr. STOKES. Thank you. Let me go back to Dr. Lenfant, the Director of the National Heart, Lung, and Blood Institute. Doctor, you mentioned earlier that we have discussed some of these issues for a number of years. One of the main diseases that we have had a great deal of discussion about over the years is sickle cell disease. I would be interested in knowing if any type of a gene therapy approach is being used now in the treatment of sickle cell disease. Generally, what are they?

Dr. LENFANT. It has not evolved yet to being done in patients, but the Institute is initiating this year, a research program on gene therapy of sickle cell disease. The primary work has been somewhat lengthy, very studious, but also very fruitful. It has brought the research community to a clear recognition that now they have the tools to develop gene therapy for sickle cell disease.

I think the cost of this new program will be on the order of $3 to $4 million a year. All the experts in this area have great expectations and think that it is an avenue which has the potential to be successful, but much research needs to be done and we are doing it.

Mr. STOKES. Are there many sickle cell disease clinical trials under way?

Dr. LENFANT. Yes. In fact, this year we have initiated a clinical trial which is an area of considerable clinical importance. As you may know, Mr. Stokes, many of the youngsters who have sickle cell disease have a very high risk of stroke and the problem is, how can we predict who is going to have stroke.

Following some research which we have supported, we think we now have a possibility to predict stroke. So we have initiated a clinical trial to assess the validity of this technique.

If it is successful, it will be a step forward of great significance; almost as great as the one that we had when we demonstrated the importance of penicillin treatment in infants.

PREVENTION INITIATIVES

Mr. STOKES. Thank you.

In the few remaining minutes that I have, let me get back to Dr. Grady of the Neurology Institute.

Dr. Grady, with health care reform looming on the horizon and with the high concentration of interest in health care reform and in prevention as an essential element of health care reform, I would be interested in knowing what prevention initiatives currently exist in your Institute.

Dr. GRADY. The major areas that we can address right now in terms of prevention are areas of stroke, specifically prevention of certain types of stroke. By the end of the decade, we expect to be able to prevent up to 80 percent of all strokes. In the area of——

Mr. STOKES. We would be able to prevent 80 percent.

Dr. GRADY. Eighty percent, yes, by the year 2000. And there are several types of strokes that we can prevent now. I mentioned several studies related to atrial fibrillation and other forms of ischemic stroke as well as hemorrhagic stroke have shown that these strokes can be prevented by identification and modification of risk factors. We also expect to be able to prevent the extent of disability following spinal cord injury and head injury.

We already can do that to some extent in spinal cord injury because, if we get people to the hospital right away, we do have a treatment for spinal cord injury that decreases disability by up to 30 percent in many individuals. That, again, will impact on the health care system because those individuals affected by trauma are typically young adults and will spend the rest of their lives in wheelchairs unable to use either lower or upper limbs or both. And so that is an area we are concentrating on.

Another area is the area of children and developmental disorders. We have discovered many things which will either prevent birth defects, or allow us to treat children immediately afterwards to prevent the extension of disorders that occur in early childhood. Those are the main areas that we feel we can prevent, in addition to the area of neurodegenerative disorders that I mentioned earlier which strike middle to older adults who then go on to prolonged disability. These are the main areas in which we feel we can make an enormous impact on the health care system.

BIOTECHNOLOGY

Mr. STOKES. Is increased research in biotechnology essential to your Institutes research activities?

Dr. GRADY. Yes, sir. Let me frame that in the guise of one of our "failures." It took over 10 years to find the gene for Huntington's disease. That was a very long and disappointing search. Earlier it was identified to be at the tip of chromosome 4. It still took 10 years and, therefore, it was very exciting when we found it; and that is another whole story you have already heard.

But during the time of the search and the constant failures trying to find that gene, 14 different technologies were developed that have escalated the whole field of genetic research. So that although it took 10 years to find the Huntington's gene, many others were found along the way and the whole field has benefited greatly from that.

Mr. STOKES. Mr. Chairman, it is unfortunate that we don't have more time to devote to really listening to these three people. They are so informative and there is so much to be learned from them. I appreciate it very much.

I yield back.

EPILEPSY RESEARCH

Mr. PORTER. Thank you, Mr. Chairman. I think these questions will go very quickly. Dr. Grady, what progress have you made in the last year regarding epilepsy?

Dr. GRADY. Mr. Porter, we have been very fortunate in the area of epilepsy. The first new drug in 15 years, Felbamate, was approved by the FDA this past year. That was a drug that was tested within our program and is now available to the general public and it is important in several ways not just for the drug alone. The approval of this drug is important, but it heralds the era of a new class of drugs that both stimulate neurons and inhibit neurons.

There are several other candidates in the pipeline of this category of drugs. Felbamate is effective for the largest population of seizure disorders, partial seizures. And it is not only effective, but it has a decrease in the side effects with which we are familiar—the wearing off of the drug, the drowsiness, et cetera that affect many people who take drugs for epilepsy. That means that the quality of life will increase for the 2.5 million people with epilepsy, or the portion of them that can take the drug.

It means that for example adults who could not drive cars will probably be able to do that now, hold down jobs of a different sort than they could or do so more successfully; children will learn better in school and go on to be more productive adults and we will benefit greatly from this.

A second finding I alluded to earlier is that of prevention of long-term seizures in children who have febrile seizures. Without treatment about 50 percent of children who have febrile seizures go on to develop seizure activity in their lifetime. Giving a drug that is commonly known, Valium, during that early period of the first seizure will prevent most of those children from going on to a lifetime of seizure activity.

Those are just two of the breakthroughs that I would like to mention to you.

Mr. PORTER. Two very exciting discoveries. The Epilepsy Branch Chief position has been vacant since last August. What is the status of the effort to fill that position?

Dr. GRADY. We do have a candidate selected for the position, and that paperwork has gone forward. As you know, we are under a freeze and must request an exception to the freeze—that is a level 15 position and to fill a positions of 13 and above, we are frozen. So filling the vacancy is in that process.

STROKE RESEARCH

Mr. PORTER. Are you conducting any research on the genetic aspects of stroke, and if so, are you coordinating with the Genome Center?

Dr. GRADY. We currently have an interest in pursuing the genetic aspects of stroke related to areas of hypertension. We are not funding large studies to do that, but some of the subanalyses that are coming out are pointing in that direction and we do keep in very close touch, as you may imagine, with the Human Genome Center.

NARCOLEPSY RESEARCH

Mr. PORTER. The National Institute of Neurological Disorders and Stroke is the major Institute which focuses on the study of narcolepsy. Can you describe NINDS programs in narcolepsy research?

Dr. GRADY. We do have a substantial program in narcolepsy, and we are focusing on the neurobiology of narcolepsy. There are animal models which are being used to study this disorder, and there is some progress in trying to find a genetic basis for the disorder. There is a great deal of interest and enthusiasm from the small but competent number of narcolepsy researchers out there. So we are optimistic that there will be breakthroughs in this area.

FUNDING LEVEL

Mr. PORTER. Thank you, Dr. Grady.

Dr. Cassman, the President is proposing a 3.7 percent increase for NIGMS—a cut of four-tenths below the inflation level. In your professional opinion is this an acceptable level of funding?

Mr. CASSMAN. We can do a great deal with it and we certainly hope to, as I said earlier. As I heard my colleagues say, we would like to be able to support grants up to the 40th to 45th success rate. Perhaps the best answer I can give you is a quote from a former Member of this body who said that "the possibilities of science are limitless, but a prudent government has to count its cost." He said this in 1886, which just shows that in over 100 years, not a great deal has changed.

BIOTECHNOLOGY INDUSTRY

Mr. PORTER. What contribution has NIGMS made to the biotech industry?

Mr. CASSMAN. I think we have made a great contribution. Most of the technologies and many of the concepts that have been used in the biotech industry have come out of the basic research that is generated by grantees of the NIGMS. A recent trade publication for the biotechnology industry listed four recent trends that they saw in biotechnology and for every one of those, including rational drug design, antisense technology, carbohydrate synthesis, and combinatorial chemistry, NIGMS has had and continues to have major research efforts. This is one of the few industries, maybe the only one, that draws directly on the research base for its development. And much of the research base, I believe, is provided by the NIGMS.

Mr. PORTER. Thank you, Dr. Cassman. Thank you, Mr. Chairman.

PARTICIPATION BY HISPANIC INSTITUTIONS

Mr. BONILLA. Mr. Chairman, I have a couple remaining questions. I heard in my absence that Mr. Stokes was asking questions about an area that I am interested in, the Minority Biomedical Research Support Program and the MARC program, the Minority Access to Research Careers.

Last year, there were 23 Hispanic institutions, Dr. Cassman, who participated in this and I want to know if that number has changed this year.

Mr. CASSMAN. It depends on the level of Hispanic population you measure. For those institutions that have Hispanic student populations greater than 25 percent, the number is still 23 of those. For those with Hispanic student populations between 15 and 25 percent, there are an additional eight. It depends on where you take your cut. Given what I believe represents a significant Hispanic student population, it would total 31 institutions.

HISPANICS AND STROKE

Mr. BONILLA. Dr. Grady, last year I asked about Hispanics and the high incidence of strokes and Dr. Goldstein told me that the Institute was exploring the Hispanic population, mainly when the Hispanics are subject to stroke. He went on to say that the study is currently going on. Could you update me on the status of that study, please?

Dr. GRADY. That study is still going on, Mr. Bonilla. We have found that Hispanic populations have a higher incidence of diabetes as a risk factor for developing stroke, and for them like other populations, at the time of the stroke, if the blood sugar is elevated, there is higher morbidity and mortality.

There is a study going on to regulate blood sugar at the time of admission to the hospital. Unfortunately, clinical trials and studies take several years to be able to analyze the data. But the studies that were done previously in animal models are very encouraging. This will be very helpful. Part of the advantage now is because stroke is identified as an acute emergency situation and patients are getting to the hospital within the first two hours of having a stroke and we can intervene at the time that it is important. Hopefully I will be able to report back to you a positive result or the result, anyway, hopefully a positive result in the future in that area because it is very critical.

Mr. BONILLA. So then you anticipate it to be completed shortly.

Dr. GRADY. Within the next two years we expect that.

DECADE OF THE BRAIN

Mr. BONILLA. On another issue, Dr. Grady—you know I have an interest in the Decade of the Brain Project and I would like a status report on the progress.

Dr. GRADY. The Decade of the Brain initiative was started in the beginning of this decade and we are making very fast progress toward the accomplishment of the goals. However, we are doing this in a time of constrained resources so that we may not be able to reach all of the goals by the end of decade.

It is interesting in that we are at a time when the neurological sciences are exploding because of the interests and possibilities such that we have been fortunate enough in even these difficult times to attract an enormous number of new researchers into the area.

The Society for Neuroscience meeting last year had 23,000 people attending who have interest in the neurological sciences. We have the talent and we are moving forward. We will move faster or slower depending on what resources are available.

ASTHMA RESEARCH AND EDUCATION

Mr. BONILLA. It is exciting to hear about the explosion of interest in that area and we will do what we can in this committee. There is a Dr. Pamela Wood, Dr. Lenfant, in the Department of Pediatrics at the University of Texas Health Science Center in San Antonio who identified two factors that caused the greatest impact of asthma among Hispanic children. They were the presence of a smoker in the household and lack of family knowledge about asthma in general.

Dr. Wood recently received a million-dollar Federal grant to expand this pilot study. My question related to that is what activities is your Institute conducting on asthma in minorities and particularly the population that I am referring to here?

Dr. LENFANT. Well, we have a very substantial research program to improve dissemination of information to reach out into the communities. We do have some programs which are specifically directed to the Hispanic community. In fact, Dr. Woods' research in San Antonio is supported by the National Heart, Lung, and Blood Institute.

Asthma, as you know, is a very common condition, but particularly prevalent in the minority population. This is the reason why we have such a focus for this activity.

Our studies span from very fundamental—looking at genetic determinants of asthma, to improving the communication of information to the patients, and helping them to take care of themselves.

Asthma is a condition which is very prevalent. There are something like 10 or 11 million people in the United States with asthma. I dare say that no one should really die from this condition if people knew what to do. And during the last few years the Institute has sponsored a program called the National Asthma Education and Prevention Program, the goal of which is to disseminate the information which is available, to help the individuals with asthma, as well as their families.

The thrust of this program is to teach the adults and children with asthma to lead a normal life, to help themselves with what we call self-management, people taking care of themselves. We do have substantial evidence that once you put in place self-management programs, you reduce considerably the morbidity of asthma and particularly emergency hospitalization.

Mr. BONILLA. Very good and a final comment for the record, you should know that in south Texas all of you have a tremendous advocate, Dr. John Howe, who runs the U.T. Health Science Center. I hope you appreciate how he is out there advocating biomedical research. Thank you.

Mr. SMITH. Thank you all. We will adjourn the meeting until 2:00 o'clock.

[The following questions were submitted to be answered for the record:]

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

WOMEN'S HEALTH INITIATIVE

Mr. Smith: What is your professional judgment about the Institute of Medicine's recommendation that the Women's Health Initiative shift its focus to the impact of diet modification and hormone replacement on cardiovascular disease?

Dr. Lenfant: To limit the Women's Health Initiative (WHI) to a study of diet modification and hormone replacement on cardiovascular disease would be undesirable for several reasons. First, there is very strong indirect and strong direct evidence that diet-induced cholesterol reduction reduces the rate of coronary heart disease; a very large trial limited to this question is probably not justified. Second, the evidence for a relationship of diet with breast cancer is quite suggestive but less so than for coronary heart disease. This question does merit a clinical trial. Third, the ultimate assessment of the place of post-menopausal therapy will depend on the balance of its effects on cardiovascular disease, cancer, and osteoporosis, so that information on as many of these endpoints as possible is desirable.

Mr. Smith: Would this duplicate information from your PEPI hormone replacement trial?

Dr. Lenfant: The PEPI study will provide information on hormone effects on cardiovascular risk factors while the WHI focuses on actual cardiovascular endpoints; thus the studies are complementary and not duplicative.

GENE THERAPY

Mr. Smith: Your Institute has had a strong presence in gene therapy research on the NIH campus. How do you invision those efforts meshing with the work of the new intramural program at the National Center for Human Genome Research?

Dr. Lenfant: Because three of the young scientists in NCHGR trained in NHLBI, there are good collaborative interactions which we expect to increase. Dr. Morgan (NCHGR) and Dr. Safer (NHLBI) are continuing their collaboration on hemophilia gene therapy that was initiated when Dr. Morgan was in NHLBI. These investigators, and others in NCHGR will want to utilize the NHLBI non-human primate facility at 5 Research Court, Rockville, MD, for safety and other studies in non-human primates before initiating studies with patients. Also, we anticipate that the patient care units managed by NHLBI, which maintains a major clinical research effort, will be utilized for collaborative clinical protocols. The central facilities maintained by the NCHGR will in turn facilitate the laboratory research of NHLBI scientists. Thus, there should be good synergism between the clinical and non-human primate facilities and expertise of the NHLBI and the central facilities for basic research of the NCHGR.

Mr. Smith: Your budget justification was the only one in NIH to mention efforts to improve management of your Institute consistent with reinventing government objectives. Can you tell us more about the actions you have taken and what savings, in staff and budget, you expect as a result?

Dr. Lenfant: As stated in the budget justification, the Institute is seeking new and different ways to manage its programs and implement the recommendations of the National Performance Review. A committee of senior Institute staff--the BOLD Committee--has enlisted the help of many Institute employees to find ways to save dollars, FTEs, change the supervisor to employee ratio, and enhance the effectiveness of our programs. The Committee has made recommendations to improve human resource management, to streamline the organizational structure, to improve information systems, to simplify managerial approval processes, to achieve greater consistency and better service in administrative management areas, and to simplify the review of grant applications.

To date the parameters governing change have been identified, and the details are being worked out with staff involvement and input. It is not possible to quantify exact savings at this point, but we know they will be achieved. For example, we expect reductions in GS-14 and above positions through attrition and re-engineering of job functions. We also expect reductions in overall employment through attrition. There are likely to be savings in printing costs, travel costs, and services such as graphic arts services in addition to savings from salaries and benefits. However, the focus is not on savings alone, but also on making the Institute as effective and well managed as possible.

Mr. Smith: Why is the average cost of your new non-AIDS grants in 1995 expected to increase by more than the biomedical research deflator?

Dr. Lenfant: The FY 1995 estimate for competing non-AIDS grants increases more than the BRDPI because of the way in which increases in average cost are calculated. AIDS grants are projected to increase less than the BRDPI. Therefore, when AIDS-related grants are included the average cost is close to the 4.1 percent BRDPI increase. The NHLBI will adhere to the NIH cost management plan in the award of competing research project grants.

SLEEP CENTER

Mr. Smith: Will the sleep disorders research center conduct research directly or only support extramural research grants?

Dr. Lenfant: The National Center on Sleep Disorders Research will not conduct any intramural research at NIH. Its major functions will be to support extramural research, conduct education and public awareness programs in sleep, coordinate and serve as a focal point for sleep research across the Federal government and with private organizations.

Mr. Smith: When do you expect the first grants to be awarded?

Dr. Lenfant: The NCSDR is currently soliciting applications for a new program to study the cardiovascular consequences of sleep apnea, which should provide new insights into whether sleep apnea is a independent or contributing risk factor for the development of cardiovascular disease. This new grant program will begin in September 1994.

BONE MARROW TRANSPLANTATION

Mr. Smith: Is your intramural bone marrow transplant unit fully operational?

Dr. Lenfant: Yes, it opened in November 1993.

Mr. Smith: How many bone marrow transplants do you expect to perform at the Clinical Center annually?

Dr. Lenfant: We expect to perform about 40 bone marrow transplants annually.

Mr. Smith: Does NIH support the entire cost of these transplant procedures?

Dr. Lenfant: Yes, the entire cost is from the NIH budget except for the patients' travel expenses and the costs for their accommodation outside of the Clinical Center during periods when the patient does not need to be hospitalized.

Mr. Smith: How much is budgeted for 1995?

Dr. Lenfant: The average cost for a single transplant is about $150,000 with a range between $75,000 and $200,000.

Mr. Smith: Are you renewing the contract for the National Marrow Donor Program in 1994:

Dr. Lenfant: Yes, the new contract is expected to be signed on or about June 28, 1994.

Mr. Smith: Will the contract be open to competing bids?

Dr. Lenfant: The Request for Proposals was released as sole source because the Institute believed that there was no other organization equipped to manage the contract. Nevertheless, it was advertized in the Commerce Business Daily, as required, and there was at least one request for a copy of the RFP. If one or more additional proposals had been received, all would have been reviewed competitively. The National Marrow Donor Program, Inc., submitted the only proposal.

We should note that the House version of the Organ Transplantation Reauthorization Bill includes a provision to transfer the Marrow Donor Program to the Health Resources and Service Administration. The Public Health Service is in favor of this transfer, and in fact intends to transfer the program, however, we do not believe this legislative change is necessary since it can be accomplished administratively.

Mr. Smith: Identify 1993-1995 estimated spending for the National Marrow Donor Program from all sources, including your Institute, the U.S. Navy, patient fees, charitable contributions and interest.

Dr. Lenfant: The following table provides this fiscal information. The 1994 and 1995 data are estimates in all cases.

Source	FY 93	FY 94	FY 95
NHLBI	$16,235,000	$15,250,000	$15,250,000
U.S.Navy	20,200,000	20,200,000	20,200,000
Total	36,435,000	35,450,000	35,450,000

The National Marrow Donor Program, Inc., fiscal year runs from May 1 to April 30 and does not coincide with the Federal fiscal year.

Source	5-1-92 to 4-30-93	5-1-93 to 4-30-94	5-1-94 to 4-30-95
Patient fees	$23,533,000	$29,061,000	$30,971,000
Interest	149,000	217,000	180,000
Charitable Contrib.	1,085,000	1,088,000	1,200,000
Total	24,767,000	30,366,000	32,351,000

Mr. Smith: Identify the current number of donors in the National Marrow Donor Program Registry, separately identifying the number of minority donors and their share of the donor pool as compared to their share of the general population.

Dr. Lenfant: The information requested is tabulated below. It is important to recognize, however, that the relative diversity of the HLA or tissue types found in various racial and ethnic groups may be such that donors in strict proportion to the U.S. population may not provide similar access to matching donors for transplants. For equivalent access, the numbers needed may be much larger or, in some cases, even smaller than for Caucasians.

Group	Number of Donors	Percent	U.S. Population	Percent
Caucasian	798,147	66.1	212,912,000	83.5
African-American	67,555	5.6	31,635,000	12.4
Asian-American	50,774	4.2	8,401,000	3.3
Hispanic	70,811	5.9	24,238,000	9.5
Native American	13,838	1.1	2,134,000	0.8
Other	6,748	0.6		
Unknown	199,900	16.6		
Total	1,207,773		255,082,000	

Mr. Smith: How many donors are identified in other U.S. Registries?

Dr. Lenfant: The only other U.S. registry with a significant number of donors is the American Bone Marrow Donor Registry, and they do not provide us with routine activity reports. The best information we have at present is that they have about 43,000 prospective donors in their registry.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject matter of research centers supported in 1994.

Dr. Lenfant: In FY 1994 the NHLBI plans to support 69 centers in 13 research areas including: acute lung injury (6); arteriosclerosis (7); cardiopulmonary disorders during sleep (3); chronic diseases of the airways (3); coronary and peripheral vascular diseases, heart failure, and congenital heart disease (10); cystic fibrosis (4); hypertension (6); occupational and immunologic lung diseases (4); pediatric cardiovascular disease (2); respiratory disorders of neonates and children (7); sickle cell disease (10); thrombosis (4); and transfusion medicine (3).

Mr. Smith: Identify 1993-1995 projected spending on the following: asthma, sickle cell anemia, cystic fibrosis, Cooley's anemia, transfusion medicine, tuberculosis, hemophilia, hypertension, and the sleep disorders research center.

Dr. Lenfant: Funding estimates for these research areas are shown on the following table:

	FY 1993 Actual	FY 1994 Estimate	FY 1995 Estimate
Asthma	$46,656,000	$42,260,000	$48,450,000
Sickle Cell Anemia	38,153,000	46,400,000	48,400,000
Cystic Fibrosis	20,537,000	21,600,000	22,400,000
Cooley's Anemia	14,299,000	15,100,000	15,700,000
Transfusion Medicine	35,997,000	43,500,000	45,100,000
Tuberculosis	4,565,000	5,100,000	5,300,000
Hemophilia	12,685,000	15,000,000	15,600,000
Hypertension	128,437,000	135,100,000	140,100,000
Sleep Disorders Research Center	2,690,000	2,848,000	3,966,000

NATIONAL CENTER ON SLEEP DISORDERS RESEARCH

Mr. Porter: Will the Center work with other Institutes and agencies to support joint research and public awareness initiatives, and will you describe these?

Dr. Lenfant: Yes, the NCSDR has taken the lead in developing a NIH-wide program announcement on sleep, which identifies many new basic and clinical research opportunities, and will serve as a stimulus for new research in this multi-disciplinary field. Applications responding to this program announcement will serve to both strengthen and expand ongoing sleep research at NIH. The NCSDR is collaborating with other agencies to support joint research. For example, it is working with NASA to develop and support joint programs in sleep, prolonged shift work, human performance, sleep loss and fatigue both on earth and in the microgravity environment.

The NCSDR plans to conduct a strategy development workshop in June 1994 to plan for a national sleep education program. The workshop will include representatives from the Department of Transportation, Department of Defense, Department of Veterans Affairs, Department of Commerce, Department of Labor, Centers for Disease Control and Prevention, and the National Aeronautics and Space Administration. The workshop will provide recommendations for both public and professional education and we are hopeful that other federal agencies, professional and voluntary organizations in cooperation with the NCSDR will begin to implement some of the recommendations beginning in FY95. The NCSDR is also working with the Federal Highway Administration in the Department of Transportation to assist with the scientific and technical review of a proposal to examine the incidence of sleep apnea in commercial motor vehicle carriers. We anticipate that this will be the start of joint research and education activities related to sleepiness, fatigue and sleep disorders as they relate to traffic accidents. In addition, the NCSDR is working with the National Institute on Child Health and Human Development on a public awareness campaign related to sleep position and Sudden Infant Death Syndrome.

Lastly, the NCSDR has begun to coordinate sleep related research across the Government with the appointment of members and ex officio Federal representatives to the Sleep Research Advisory Board. The Board will assist the NCSDR in identifying research priorities and developing plans for coordinating sleep and sleep disorders research across the Federal Government and with other private organizations. The first meeting of the Board will take place in the summer of 1994.

SLEEP DISORDERS CENTER

Mr. Porter: Please submit for the record a description of the Center's budget for 1994, and will you give us an idea of the Center's budget needs for 1995?

Dr. Lenfant: The estimate for sleep disorders research is $13,300,000 in FY 1994. This amount includes funds for extramural grants and contracts for sleep research as well as administrative costs for the Sleep Disorders Center. In FY 1995 the NHLBI plans to increase funding for sleep disorders research to $17,300,000.

SICKLE CELL DISEASE

Mr. Stokes: Is the level of knowledge needed to understand the disease there, or is there additional basic research that needs to be pursued? If so, describe the basic research and the funds needed for investment in this area?

Dr. Lenfant: Occlusion of the blood vessels causes the major adverse clinical manifestations of sickle cell disease and accounts for much of the morbidity and mortality associated with this disease. Despite significant advances in the basic science of sickle cell disease, however, the pathology associated with occlusion of the blood vessels remains ill defined and the subject of much speculation. Factors contributing to the initiation of vascular occlusion may include abnormalities of blood flow related to sickling, abnormal adhesiveness of sickle red blood cells to blood vessel walls, loss of water and poor deformability of sickle red cells, various vascular factors, and activation of the blood clotting systems. Abnormalities in the blood clotting system have been implicated in stroke, acute chest syndrome, pulmonary hypertension, and miscarriage in sickle cell disease patients. Despite evidence of a role for these factors in vascular occlusion in sickle cell disease, existing data leaves important questions unanswered. Understanding the role of these factors in sickle cell disease pathology is likely to facilitate the rational design of therapeutic approaches and to thereby improve clinical care of affected individuals.

Another area of sickle cell research that requires further investigation is the molecular biology of the switch from fetal to adult hemoglobin. This area has important clinical implications, because the reversal of this switch would result in the replacement of sickle hemoglobin with fetal hemoglobin, which would effectively ameliorate the clinical expression of sickle cell disease. Although major advances have occurred and continue to occur in this area, the precise mechanism of hemoglobin switching remains elusive. Investigations into interactions of protein factors with various specific regions of the hemoglobin genes is likely to shed light on this important mechanism. Elucidation of the hemoglobin switching mechanism could lead to the design of pharmacological agents that would increase the production of fetal hemoglobin and greatly alleviate the symptom of this chronic and disabling disorder.

Mr. Stokes: What sickle cell Disease Clinical Trials are underway?

Dr. Lenfant: We support a number of important clinical trials in sickle cell disease. The phase II trial of penicillin prophylaxis (PROPS II) is currently underway to determine at what age prophylactic penicillin can be safely discontinued. Currently young infants are placed on prophylactic penicillin soon after birth to prevent life threatening infections. PROPS II will end in August, 1994. The Multicenter Study of Hydroxyurea in Sickle Cell Disease (MSH), examines the use of hydroxyurea in severely affected adult patients. Patients receive either hydroxyurea or placebo to determine if the rate of painful episodes can be reduced by 50%. This trial is now entering its fourth year. Four of the Comprehensive Sickle Cell Disease Centers have undertaken a small pilot phase I study of hydroxyurea in pediatric patients to determine if the dose of hydroxyurea that is effective in adults will be effective in children, and if this drug will adversely affect growth and development.

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) begins in 1994 and will determine if the occurrence first stroke in high risk children can be significantly reduced by prophylactic transfusion. Stroke occurs in 7-8% of children with sickle cell disease, and the rate of recurrence is 46-90% unless the children are chronically transfused. The rate of recurrence can be reduced to 10% by chronic transfusion, but no studies have demonstrated an effective method to prevent the first stroke. Children will be screened with transcranial doppler ultrasound to determine if there is evidence of obstructed cerebral vessels, which places them at high risk for developing a stroke. The children will then be randomized to receive chronic blood transfusion therapy or the currently available supportive care.

IMPACT OF LEVEL FUNDING

Mr. Stokes: According to the Congressional Justification, the Institute would support 2,689 research project grants in FY 1995, 21 fewer than currently funded. This compares with 2,710 in FY 1994, and 2,697 in FY 1993. Would you translate for us what this relatively flat line in the number of research project grants supported means in terms of any limits it might place on opportunities for improving the quality of life?

Dr. Lenfant: Of course we regret the need to reduce the number of research project grants in fiscal year 1995. Although this plateau in the number of grants may mean that some research may not proceed as quickly as we would like, we nevertheless expect to be able to maintain the momentum of our research effort. Science has advanced to the point where there are unprecedented opportunities for improving the health and wellbeing of the American people. There is no question in my mind that new curative and preventive approaches are on the immediate horizon. The issue is not whether we will achieve our goals, but when.

ASTHMA

Mr. Stokes: There have been numerous articles on why persons suffering from asthma should exercise, as opposed to the thought years ago that asthma sufferers should refrain from exercising. Doctor, what has research taught us about the relationship between asthma and exercise?

Dr. Lenfant: Exercise-induced asthma, or narrowing of the airways minutes after exercise, occurs in almost all asthma patients. It is thought to result from the cooling and subsequent rapid rewarming of the airways after a period of exertion. In 1994 the NHLBI is initiating a research program on physical activity and cardiopulmonary health to investigate the effects of physical activity on respiratory health and fitness in patients with asthma.

Persons with asthma, like everyone else, should participate in exercise for cardiovascular fitness. Before treatments were available to control asthma, even modest amounts of exercise could bring on asthma symptoms. However, today there are several medications available to prevent the onset of symptoms. In addition, medication is available that can be used to treat bronchoconstriction when it occurs. The Guidelines for the Diagnosis and Management of Asthma, published by the National Asthma Education and Prevention Program (NAEPP), emphasize that one of the goals of therapy is to allow the patient to fully participate in all activity, including exercise. Exercise is particularly important in children. In the research program, "Interventions for the Control of Asthma in Black and Hispanic Children," the five participating centers emphasize to families that children with asthma should participate in exercise and sports. Moreover, the NAEPP has focused on the importance of exercise in a video for physical education instructors and for patients with asthma in several of its "Healthbeat" programs, a syndicated news/health feature that is aired on over 800 African-American radio stations.

Mr. Stokes: What progress is being made on new treatments that will reduce or eliminate the clinical symptoms of asthma?

Dr. Lenfant: It is now recognized that asthma is a complex chronic lung disease of varied etiology triggered by a number of factors such as allergens, drugs, chemicals, exercise, cold dry air, infections and emotions, making asthma therapy difficult and sometimes complicated. Multiple medications are often required, including medications to treat and control respiratory symptoms as well as medications to control the underlying inflammation. Basic research investigations are leading to multiple new approaches for the treatment of asthma but new treatments require well controlled clinical trials to assure safety and efficacy. This is particularly important because asthma is a chronic condition and medication use is often required for long periods of time.

In 1994, the Institute initiated an Asthma Clinical Research Network, consisting of a data center and five clinical centers, which have access to large numbers of asthmatic individuals, of all ages, both male and female. In each clinical center, at least one-third of the asthma patients in the investigation will be minority. The network provides a mechanism for the rapid evaluation of new medications and for assessing current treatment strategies as well as to assure rapid dissemination of clinical findings to the health care community. Some of the medications that are expected to be studied are high dose inhaled steroids, used to control inflammation in moderate and severe asthmatics, non-steroidal anti-inflammatory medications, long acting bronchodilator medications, and leukotriene inhibitors a new class of anti-asthma medications which appear to hold considerable promise.

The NHLBI also supports the Childhood Asthma Management Program to determine, in a population of 944 asthmatic children 5-12 years old, if regular use of either of two types of inhaled anti-inflammatory medications results in greater lung function and less bronchial hyperresponsiveness, patient morbidity, and use of health care resources, and improved quality of life over a five year period. The study is expected to yield important information regarding the effect of asthma treatment on many important aspects of growth and development, and may answer questions about asthma changes during puberty and adolescence. It will also ensure that therapeutic recommendations are based on scientifically sound studies that include patients from a broad representation of racial and ethnic groups.

MOLECULAR BIOLOGY

Mr. Stokes: Can you highlight for us what advances could stem from increased investments in molecular biology, as it relates to the diseases and disorders under the purview of your Institute?

Dr. Lenfant: By providing new avenues for the diagnosis, detection, prevention, treatment, and cure of human diseases, molecular biology has tremendous potential for a broad impact on public health - in terms of morbidity, mortality, and cost. Molecular biological techniques and strategies have a broad impact on numerous areas of basic, applied, and clinical research. I will highlight four key areas whose continued success hinge upon molecular biological approaches:

Genetically Engineered Molecules: Genetic engineering relies upon the ability to combine genetic material (DNA) from different sources to produce and isolate biologically active compounds. Initial efforts focused on producing compounds that exist in nature in only trace amounts, such as tissue plasminogen activator (TPA) to treat and prevent heart attacks; factor VIII for hemophilia; and DNase for cystic fibrosis. The field is now focusing more and more attention on producing therapeutic molecules that don't exist in nature. For example, intense efforts are attempting to alter TPA so that it is more effective at lower doses, thereby avoiding side effects, such as hemorrhage. Future investments in this area will permit the creation of new molecules to prevent and treat heart, blood vessel, lung, and blood diseases and to conduct clinical trials that will test their efficacy.

Genetically Altered Animals: Genetically altered animals are revolutionizing the study of human disease. Naturally occurring animal models that mimic human diseases occur rarely. Genetically altered animal models are now being produced that mimic human diseases. Examples include mouse models for cystic fibrosis, pulmonary hypertension, sickle cell anemia, and atherosclerosis. In addition to studying the cause and progression of the disease, these animals are used to develop and test extremely promising and progressive treatments for cure, e.g. gene therapy, that cannot be done in humans.

Gene Therapy: Gene therapy offers tremendous potential for the prevention, treatment and cure of a broad range of diseases, whose economic and social toll are immense. Current human gene therapy trials include treatment of familial hypercholesterolemia and cystic fibrosis. Promising studies are also underway to use gene therapy to treat other heart, lung, and blood diseases, such as sickle cell anemia, hemophilia, and familial emphysema. Studies to determine the efficacy of gene therapy approaches to the treatment of acute lung injury and Adult Respiratory Distress Syndrome are just beginning to be explored. Despite these successes, gene therapy is still in its infancy. New efforts are needed to investigate the selection of appropriate target cells, develop improved vehicles (vectors) for delivering and inserting new genes into these cells, design methods to insure appropriate expression and regulation of the inserted gene, and create appropriate animal models to test these parameters.

Identification of Genes Responsible for Disease: Very prevalent diseases, e.g., hypertension, stroke, atherosclerosis, anemias, thrombosis, asthma, and obesity are considered to be "complex" because the effects of several different genes, together with environmental factors, are required to produce these diseases. Technologies relying on molecular biological tools offer an unprecedented opportunity to dissect out the genetic basis of these diseases. The likely benefits are many. Researchers will be able to delineate the mechanistic basis for the cause and progression of a disease, so that clinicians will be able to treat the cause, instead of the symptoms. Treatments will become more tailored to the individual, by choosing from existing therapies or by developing new targeted and specific interventions. It will also be possible to identify individuals at risk for developing the disease before clinical symptoms appear, allowing new and more targeted possibilities for prevention. The impact of such preventive measures could be far-reaching, since modification of behavior or environment is likely to be more cost effective than life-long drug therapy.

HIGH BLOOD PRESSURE

Mr. Stokes: What new research initiatives are being supported in high blood pressure, a major risk factor for heart disease and stroke?

Dr. Lenfant: In the last fiscal year, the Institute started several initiative, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; dietary approaches to stop hypertension; improving hypertensive care for inner city minorities; obesity prevention in American Indians; and a hypertension in minorities database.

This fiscal year, the Institute will begin a program entitled "Physical Activity Intervention in Health Care Settings for High Risk Sedentary Adults". This study will include an assessment of change in blood pressure that is associated with an increase in physical activity.

Two new initiatives on the molecular genetics of high blood pressure have been released to the scientific community within the past few months and will provide research funding to begin in fiscal year 1995. The first initiative, entitled "Genetic Determinants of High Blood Pressure", is designed to coordinate efforts to map and identify the major genetic factors involved in the development of essential hypertension, or high blood pressure. The second initiative, entitled "Specialized Centers of Research (SCOR): Molecular Genetics of Hypertension", is focused primarily on the analysis of the mechanisms by which various combinations of genes can result in the development and maintenance of chronic high blood pressure.

Mr. Stokes: In your professional judgment, what research opportunities and what outreach opportunities are on the horizon that should be supported, but must be postponed because the fiscal year 1995 request cannot support them?

Dr. Lenfant: In my professional judgement, we do have opportunities that could be pursued if additional funds were available.

For example, the immune system is normally thought of as the body's defense against infection. However, there is mounting evidence in both humans and in animal models that the immune system may be involved in the development of high blood pressure. The mechanisms through which the immune system can affect blood pressure are not understood, and further research in this area may result in the development of novel and innovative treatments for high blood pressure.

The lack of high-resolution genetic maps in the rat is hampering investigators from identifying the genes linked to high blood pressure in rat models of the disease. Gene identification in animal models can often accelerate the determination of genetic factors responsible for disease in humans. Therefore, the Institute could fund a rat genome project to remove barriers to hypertensive gene identification in rat models of high blood pressure. The Institute could also support development of user friendly computer software that will aid investigators in the storage, retrieval, and analysis of genetic data.

Lastly, there is the possibility of funding an initiative on alternative therapies for hypertension, with a specific emphasis on the discovery of new chemical entities with potential as antihypertensive agents. This effort would combine several disciplines and products occurring in nature as well as man-made chemicals.

ATHLETE'S HEART

Mr. Stokes: Each year, we read about some athlete collapsing or dying from a heart problem. What can you tell us about how and why this can happen to an individual that appears to be in excellent condition?

Dr. Lenfant: The most common cause of an athlete collapsing or dying from a heart problem is a genetic disease known as hypertrophic cardiomyopathy (HCM). In this disease the muscle of the left ventricle thickens, particularly in the wall that separates the left ventricle from the right ventricle. This impedes the heart's ability to pump blood effectively. In some patients, this thickening is associated with abnormalities of cardiac rhythm and can result in sudden cardiac death. Although affected individuals have the gene at birth, the condition may not become apparent until childhood, adolescence, or much later in life. The reason for this variation of onset is unknown.

Another more rare cause of collapse occurs in patients who have had an infection which is capable of affecting the heart and causing a condition known as myocarditis. In this condition, cells of the immune system, the lymphocytes, invade the heart, often destroying heart muscle cells, leaving the heart in a weakened condition because cardiac muscle cells are unable to reproduce and replace the dead cells. Treatment for this condition involves immunosuppression, a way of reducing the activity of the lymphocytes. In some patients the condition progresses despite all attempts at therapy and the patient requires a heart transplant.

Mr. Stokes: What progress is being made in this area?

Dr. Lenfant: We have made tremendous progress. Through research conducted and supported by the Institute, we know that HCM is genetically heterogeneous but in any given patient there is only one gene defect. The most well studied gene is found on chromosome 14. The defect causes a change in the composition of a protein that is associated with the heart's contractile function.

Until recently, the most common form of treatment involved the use of drugs to decrease the force of the heart's contraction. More recently we have found that two devices can be implanted to prevent the occurrence of sudden cardiac death. One is the defibrillator, which administers a shock to the heart when an abnormal life-threatening arrhythmia begins. The second device, only recently introduced, is the pacemaker which is set so that the left ventricle begins to contract a fraction earlier than it would normally, thus allowing blood to pass out of the chamber before the wall dividing the chambers contracts and obstructs outflow. Blood tests are available to detect whether a family member has inherited the disease and patients can be counselled as to degrees of strenuous exercise that are safe. However, not all sudden cardiac deaths occur during exercise and patients with the disease need careful examination by an expert in the field.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly.

Dr. Lenfant: Gene therapy is the introduction of a gene (or genes) into a patient's cells to provide a new set of temporary or permanent instructions to these cells. Adding a gene may be used to: (1) restore a function that is absent due to an inherited gene defect; (2) acquire a new function that is not normally present; (3) enhance a normal cell function; or (4) prevent a cell function. Consequently, gene therapy offers tremendous potential for the prevention, treatment, and cure of a broad range of cardiovascular (heart and blood vessel), lung, and blood diseases and disorders.

Cardiovascular disease targets for gene therapy include the prevention or treatment of high blood cholesterol, atherosclerosis, and high blood pressure. Other examples include strategies to repair or regenerate heart tissue damaged by a myocardial infarction; to alter the cell surface characteristics of donor hearts in order to prevent transplantation rejection; to prevent heart attacks by promoting activity that selectively digests blood clots in the coronary blood vessels without causing bleeding in other parts of the body such as the brain; and to stimulate new coronary blood vessel formation in order to increase the blood supply to the heart. An additional area of promise is the use of gene therapy to prevent artery reclosure (restenosis), a key biological process that causes human balloon angioplasty and coronary bypass procedures to fail.

Cystic fibrosis is one of the most promising pulmonary disease candidates for gene therapy. In the first human gene therapy experiments for cystic fibrosis, scientists have recently provided evidence that gene therapy can correct the underlying defect. A new direction being explored by NHLBI investigators is the use of gene therapy to accomplish short term or transient increases in protein expression for therapy of acquired disorders such as the Adult Respiratory Distress Syndrome. One approach that shows promise involves delivery of liposomes (vesicles made of lipid) to carry genes into cells. Preclinical testing of this approach in humans has just begun. This new direction has the potential for furthering progress in gene therapy for treatment of acute lung injury where even short term increases in protective antioxidants or anti-inflammatory agents could be helpful. Other future possibilities include alpha-1-antitrypsin deficiency (the inherited form of emphysema), pulmonary hypertension, neonatal and chronic pulmonary infections, and bronchopulmonary dysplasia.

A number of hematologic diseases are excellent models for gene therapy. These include severe combined immunodeficiency disorder, thalassemia, Fanconia anemia, hemophilia, lysosomal storage diseases (eg., Gaucher's disease), and sickle cell disease. Hemophilia is particularly attractive as an early target for human gene therapy because the genes for the defective proteins have been isolated and because only low levels of the functional form of the proteins are required to restore normal clotting activity.

Increased investments in gene therapy research offer much hope for making landmark advances in the diagnosis, treatment, and cure of these major heart, blood vessel, lung, and blood diseases. However, in spite of its vast potential, gene therapy is still in its infancy, facing many scientific and technical hurdles before it can achieve widespread clinical application. Important issues must be explored, including the development of effective delivery (viral or non-viral) systems capable of transferring the normal gene into a large number of cells, long term gene expression systems, the basic biology of the target cells, and the development and testing of appropriate animal models important for assuring the safety and efficacy of human gene therapy. In addition, it will be important to establish appropriate resources that form the infrastructure for the areas of scientific need and to address ethical legal and social issues as they arise.

Mr. Stokes: How much is included in the FY 1995 budget request for Gene Therapy?

Dr. Lenfant: The Institute's FY 1995 budget request includes $39,700,000 for gene therapy.

Mr. Stokes: How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Lenfant: In FY 1993 and FY 1994 the institute invested $32,042,000 and $38,200,000, respectively, in this research.

MINORITY HEALTH

Mr. Stokes: As the director of an Institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues--while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease--while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Lenfant: We share your concerns about the continuing crisis in minority health. We also recognize that despite the remarkable scientific accomplishments of the past several decades, racial disparities still exist in the diagnosis, treatment, and prevention of many diseases. Therefore, the Institute's efforts continue to be directed towards identifying the causes of these disparities and developing strategies to improve them. Recently, we have increased our emphasis further on minority-specific research endeavors. For example, new advances in sickle cell anemia have enabled the Institute to initiate a program in gene therapy to develop methods to correct or replace the defective gene responsible for this disease. A program on obesity prevention in American Indians will develop and assess school-based interventions in pre-adolescents. An ongoing study of diabetes and cardiovascular disease among Mexican Americans is comparing cardiovascular disease risk factors such as diabetes in Hispanics and non-Hispanics. In addition to supporting minority-specific programs, we continue to strive to include more minorities in all of our research study populations in order to increase the available data applicable across populations.

A Working Group on Research in Coronary Heart Disease in Blacks was convened by the NHLBI to identify research accomplishments and opportunities for the Institute to use as a basis for developing its plans for minority research support in the next several years. The Working Group's recommendations have recently been reported in a comprehensive document on basic, clinical, population-based, and behavior and prevention research. These and other activities will guide the Institute in its ongoing efforts to ensure that diverse segments of the population benefit from the results of scientific research and development.

BASIC RESEARCH

Mr. Stokes: What are some of the most exciting and most promising basic research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Lenfant: Basic research presents many exciting and promising opportunities. A few of these are as follows:

o Advances in the study of genetics are elucidating the causes and potential treatment approaches to a number of diseases, including respiratory distress syndrome of the newborn, asthma, chronic obstructive pulmonary disease, and pulmonary fibrosis.

o Developmental biology is contributing to the understanding of lung development necessary to develop effective methods of preventing bronchopulmonary dysplasia, a chronic lung disease that often affects very low birth weight premature infants.

o Progress in cystic fibrosis, such as the discovery and cloning of the gene that causes the disease, is leading to advances in both drug therapy and gene therapy, and may potentially lead to a cure for cystic fibrosis.

o Gene therapy has yielded advances in sickle cell disease that could result in a cure for this chronic debilitating disease.

o The use of soluble protein components on the surface of blood cells to induce immune tolerance may prevent adverse immune reactions in recipients of platelet transfusions, bone marrow, or organ transplants.

o Basic research in hematopoietic stem cell biology has great potential for application in genetic and acquired diseases, and in development of gene therapy to induce life-long expression of normal genes.

o Better understanding of the basic biology of immune tolerance is needed to solve the problems associated with graft-vs-host disease, a serious consequence of unrelated-donor bone marrow transplantation.

- Basic research in gene therapy for animals with hemophilia has important implications for reduction of morbidity and mortality from the disease in humans.

- Basic studies in thrombosis could answer questions about identification of individuals at high risk for thromboembolic disorders, for development of effective prevention strategies.

- Identification of a key exchange molecule and its gene, which control transport of calcium into heart muscle, could lead to development of new drugs to control the heart's contraction, as in patients with hear failure.

- Better understanding of mutations of the gene for myosin, a major heart muscle component, may lead to improved diagnosis, treatment, and prevention of lethal inherited heart diseases.

- New research in angiogenesis, the growth of new blood vessels, has developed techniques that may have the potential to prevent irreversible injury to the heart muscle in heart attacks, and possibly to prevent angina pectoris, the severe chest pain associated with coronary heart disease.

- Genetic engineering can induce adult heart muscle cells to divide and reproduce, an ability that could substantially improve healing heart muscle following a heart attack.

- New information on how blood vessels adapt to long-term increases in blood pressure is leading to improved treatment of the complications that occur with chronic high blood pressure, such as stroke and cerebrovascular disease, atherosclerosis, and coronary heart disease.

- Basic research is enabling the identification of genes responsible for high blood pressure, and this finding has potential benefits for treatment and prevention strategies in individuals at high risk for the disease and its complications.

- Genetic studies of human transplant immunology have reduced the risk of rejection of transplanted tissues in animals, and show promise for application to humans in need of compatible donor tissues.

- Recent advances in our ability to detect potential genetic defects in the embryo offer exciting possibilities for future development of procedures to correct genes responsible for congenital heart malformations.

o Recent findings from basic research on atherosclerosis suggest that development of drugs that interfere with formation of toxic chemicals may be an important means of preventing this important cardiovascular disease.

o New understanding of the immune mechanisms responsible for restenosis, or blockage of coronary arteries following successful balloon angioplasty, may lead to new opportunities to prevent restenosis.

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Lenfant: The NHLBI supports a variety of research training and career development programs to ensure the availability of adequate numbers of researchers who are trained in the use of the latest technologies and who have the capability of developing advanced technologies for tomorrow. At any given time, the Institute supports approximately 1,500 graduate students and individuals in postdoctoral training through the National Research Service Award program. All of these individuals are receiving training in areas of interest to the Institute. As new technologies emerge the NHLBI quickly incorporates them into its training programs. For example, to stimulate training and collaboration in the new areas of molecular biology, the NHLBI established the Programs of Excellence in Molecular Biology. Additionally, the Clinical Investigator Development Award provides a stable source of support for research-oriented M.D.s to pursue research endeavors germane to the Institute.

The Task Force on Women, Minorities, and the Handicapped in Science and Technology projects that by the year 2000, 85 percent of the new entrants to the nation's workforce will be members of minority groups and women. The NHLBI is supporting programs such as the Minority Institutional Research Training program, the Short-Term Training for Minority Students, Minority Access to Research Careers Summer Research Training Program, and the Research Supplements for Underrepresented Minorities to ensure that adequate numbers of minorities will also be trained in the latest technologies and prepared to make valuable contributions to the nation's research enterprise.

CLINICAL RESEARCH

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Lenfant: Currently, the Institute supports research in a variety of exciting and promising areas that will have substantial benefits for the diagnosis, treatment, and prevention of heart, lung and blood diseases. Some examples of major areas of opportunity are as follows:

- Identification of genes responsible for blood pressure regulation could lead to new treatments for high blood pressure.

- Growth factors that promote development of new blood vessels are being evaluated for treatment of vascular disorders.

- A registry of children who undergo treatment of abnormal heart rhythms by destruction of abnormal heart tissue could provide important data for assessing long-term outcome, avoiding unnecessary procedures, and preventing adverse outcomes.

- Studies of improved anti-clotting drugs have the potential for improving treatment and survival of patients with coronary heart disease.

- Studies are needed on the efficacy of balloon angioplasty in the emergency room as an alternative to clot-dissolving drugs.

- Treatment of coronary heart disease with new cholesterol-lowering drugs could prevent heart attacks and provide an alternative to surgery and other interventions for some patients.

- Studies of high cholesterol and high blood pressure in children are needed to determine whether drug treatment is safe and efficacious in prevention of cardiovascular disease.

- A network of clinical centers to study acute respiratory distress syndrome may facilitate identification of effective new treatments for this and other cardiopulmonary disorders.

- Gene replacement is an exciting new area of research with many important questions about the safety and efficacy of this approach for the treatment of cystic fibrosis.

- The increasing incidence of HIV infection in young children may be reduced if a new clinical trial shows that HIV-specific immune globulin is safe and effective for prevention of maternal-fetal transmission of the virus.

- Potential studies of hydroxyurea for treatment of sickle cell disease may determine its appropriateness for use in children, as well as adults.

- Studies of hematopoietic stem cell transplantation in animals show considerable promise for treatment of fatal genetic diseases in utero in humans.

- Further studies are needed in humans to apply existing knowledge about immune tolerance to patients who undergo unrelated-donor bone marrow transplantation, in order to reduce the morbidity and mortality associated with this procedure.

MINORITY HEALTH

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Lenfant: Approximately six years ago, as part of its participation in the DHHS Office of Minority Health Working Group on Cardiovascular Disease and Stroke, the NHLBI identified its research, research training, and outreach programs targeted to minorities. The assessment also revealed some gaps in the Institute's minority portfolio. Since that time, high priority has been given to programs designed to fill these gaps. The Institute has implemented at least one new minority research and training program each year, or revised existing training programs to make them more responsive to the needs of the minority population. Examples of research programs implemented in response to these needs include Cardiovascular Disease in American Indians, Obesity Prevention in American Indians, Smoking Cessation Strategies for Minorities, Interventions for Control of Asthma in Black and Hispanic Children, Mechanisms of Hypertension in Black Men and Women, and Improving Hypertension Care for in Inner City Minorities. Examples of training program implemented include the NHLBI Minority Access to Research Careers Summer Research Training Program, Short-Term Training for Minority Students Program, Research Supplements for Underrepresented Minorities, and Research Development Award for Minority Faculty.

The Institute's Ad Hoc Committee on Minority Populations advises the Institute on the most appropriate strategies for disseminating information to minority populations. This year, the Institute is planning a new outreach initiative targeted to the Hispanic community that will include involvement of Hispanic grass-roots organizations. The program will be pilot-tested in the Washington metropolitan area and, if successful, will be expanded to other communities and other minority populations.

Mr. Stokes: What significant initiatives in minority health research and research training and outreach are supported by your Institute?

Dr. Lenfant: NHLBI support for minority programs was approximately $132 million in FY 1993, and we expect the FY 1994 support to be at the same level. These funds supported over 500 individual research projects. Two obesity-related minority research programs--Obesity Prevention in Native Americans and the NHLBI Growth and Health Study--are particularly significant because obesity, which disproportionately affects minority populations, is a major preventable risk factor for cardiovascular disease. Other important programs include the Comprehensive Sickle Cell Centers, Phase II of the Prophylactic Penicillin Study, the Childhood Asthma Management Program, Collaborative Projects on Minority Health, Diabetes and Cardiovascular Disease in Hispanics, and the Honolulu Heart Study--all of which address diseases that disproportionately affect minority populations. In addition to the training programs mentioned in response to a previous question, other important training programs supported by the Institute include the Minority School Faculty Development Award program, the minority-specific Preventive Cardiology Academic Award, and the Junior Investigator Research Development Award.

Mr. Stokes: How does your Institute identify its priorities for investments in minority research and research training?

Dr. Lenfant: The NHLBI assessed its programs several years ago and identified several gaps in its minority portfolio that we are systematically addressing. The Institute's Ad Hoc Committee on Minority Populations and other community advisors provide advice on programmatic needs and assistance in setting priorities. Additionally, staff attend several national minority meetings where they have the opportunity to learn first-hand about the needs of the minority communities. The input received from these groups and individuals is used by staff to develop minority research and training priorities. The Institute, with advice from its National Heart, Lung, and Blood Advisory Council, incorporates these priorities into its plans for support of the national program in cardiovascular, lung, and blood diseases.

Mr. Stokes: When the Office of Research on Minority Health provides funds to your Institute, do these funds typically augment existing minority programs or efforts, or do they replace funds your Institute previously invested in its minority research and research training initiatives, elaborate.

Dr. Lenfant: Any funds received from the NIH Office of Research on Minority Health (ORMH) are used to augment existing minority efforts of the NHLBI. For example, ORMH provided about $300,000 to support the Institute's minority supplements program. The money was used to pay the last year of support for 16 supplements. The savings from this effort enabled the Institute to support more new minority supplements. The total FY 1993 cost (NHLBI and ORMH contribution) of the programs was six million dollars. This year the Institute has requested support to co-fund a workshop for recipients of minority research supplements. The NHLBI is providing support for participation of approximately 100 individuals. If the ORMH request is approved, the funds will be used to support about 50 additional participants.

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place?

Dr. Lenfant: The NHLBI made its first minority research supplement awards in fiscal year 1988, and the NIH minority supplement program began the following year.

Mr. Stokes: Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Lenfant: To date, the NHLBI has supported a total of 305 individuals through this program, 167 of whom have completed their supplement research experience. The latter number includes 78 individuals supported through the Minority Investigator Research Supplement; they constitute the subset of supplement awardees who have reached a stage in their careers at which they are expected to compete for other research support. As of March 7, 1994, we had received final progress reports on 64 of these awardees. Data indicate that 24 had received other research support: 3 have NIH regular research grants, 8 have NIH Clinical

Investigator Development Awards, 2 have American Heart Association Grants, 1 has an American Lung Association grant, 2 have National Science Foundation grants, 3 have other foundation grants, 1 has university support, and 7 have Research Development Awards for Minority Faculty.

Overall, the progress reports we have received demonstrate that individuals supported by the NHLBI Minority Research Supplements Program have benefitted from the program. Many are pursuing careers in science or medicine, and even those who have interrupted their academic training are working in health areas. The Institute is pleased to have played a role in advancing their careers.

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of Historically Black Colleges and Universities in Biomedical Research?

Dr. Lenfant: A major initiative supported by the NHLBI to increase the participation of Historically Black College and Universities (HBCUs) in biomedical research is the Minority School Faculty Development Award, which provides five years of research support to faculty at minority schools. In addition to increasing the skills of the individual investigators, the program helps strengthen the research infrastructure by developing a cadre of well-trained investigators, equipment, and an opportunity to network with scientists at nearby institutions. The Institute is developing a science education initiative targeted to HBCUs for implementation in FY 1995. The program will strengthen the science education curriculum at these institutions.

MINORITY EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Institute?

Dr. Lenfant: A total of 112 NHLBI positions are at the GS-15 level or above.

Mr. Stokes: How many employees in your Institute are in GS-15 and above positions?

Dr. Lenfant: The NHLBI has 108 employees at the GS-15 level or above; four of these positions are currently vacant.

Mr. Stokes: In your Institute, currently, how many African Americans are at the GS-15 and above level?

Dr. Lenfant: The Institute has four African American employees in positions at the GS-15 level or higher.

Mr. Stokes: In what positions are they?

Dr. Lenfant: These positions include Acting Division Director, Deputy Executive Officer, Deputy Branch Chief, and Branch Chief.

Mr. Stokes: In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Lenfant: The Institute does not have any cases pending exception to the freeze.

Mr. Stokes: Has the NIH requested relief from the freeze and if so, what was the response?

Dr. Lenfant: The NIH requested relief from the Public Health Service hiring freeze imposed in December 1993 because NIH had successfully managed its FTE ceiling. The request is under consideration by the PHS.

Mr. Stokes: If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Lenfant: The current freeze on hiring outside of PHS, and appointments and promotions to the GS-14 level and above limits the ability of the Institute to provide opportunities for advancement and to attract minorities to fill vacancies in the Institute. Lifting the freeze would help NHLBI's ongoing effort to culturally, racially, and ethnically diversify our workforce by providing more opportunities to recruit, attract, and hire more underrepresented minorities into these positions. Several recruit actions are in process that offer the opportunity to further diversify our workforce.

PREVENTION RESEARCH

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Lenfant: Although the Institute is pleased to see enormous strides made in diagnosis and treatment of the diseases that are part of its mandate, we have never lost sight of our ultimate goal -- prevention. Research to further that goal ranges from basic research on fundamental mechanisms of health and disease to large-scale clinical trials to evaluate new strategies. The latter category comprises some of the Institute's most significant and visible efforts with respect to health promotion and disease prevention. Clinical trials are often the final stage of research that occurs before new approaches are incorporated into general practice. Examples of ongoing trials include evaluation of strategies to prevent hypertension by nonpharmacologic interventions such as diet and exercise; examination of the effects of school-based interventions for promotion of long-term healthful behavior in children to reduce their subsequent cardiovascular risk; determination of the feasibility, safety, and efficacy of dietary intervention in children with elevated blood cholesterol levels; assessment of the effects on cardiovascular risk factors of hormone replacement therapy in postmenopausal women; determination of whether intake of antioxidant vitamins (C, E, and beta-carotene) reduces cardiovascular risk in women; comparison of the effects of stress reduction techniques on the control of mild hypertension in blacks; and determination of whether intensive smoking cessation efforts can reduce risk of chronic obstructive pulmonary disease in smokers who already have reduced lung function.

In addition, the Institute supports technology transfer programs in five areas to disseminate research findings and educate physicians, patients, and the public about disease prevention and control measures. The programs include the National Asthma Education and Prevention Program, National Heart Attack Alert Program, NHLBI Obesity Education Initiative, National High Blood Pressure Education Program, and National Cholesterol Education Program. The education programs are designed to raise awareness by patients, health professionals, and the public of the seriousness of the diseases; ensure symptom recognition by patients, patient families, and physicians; and promote effective disease prevention and control. Some of these programs particularly address disparities in disease among minorities, for example, the Strike out Stroke program that targets hypertensive blacks in the so-called Stroke Belt states, and a new mass media campaign targeted primarily at inner-city populations to create greater awareness of the warning signs of asthma.

BIOTECHNOLOGY

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Lenfant: Biotechnology research, like molecular biology research, has a broad impact in biology and medicine and has already played a major role in improving therapeutic modalities to reduce morbidity and mortality in cardiovascular, lung, and blood diseases. Typically, biotechnology activities encompass the use of recombinant DNA techniques, monoclonal antibody production, and gene transfer to produce and deliver products that target specific diseases or organs.

Biotechnology research has led to efficient systems for delivering large biomolecules to targeted sites within the human body for therapeutic purposes. For example, the use of gene therapy is now being studied to deliver normal genes directly into the lungs of patients with cystic fibrosis to correct the underlying defects. In addition, better therapy for hemophiliacs is now possible following the recent successful cloning of blood clotting factors VIII and IX. Despite significant advances in development of implanted circulatory assist devices, those intended for long-term use may fail because of infection or inadequate biocompatibility of the materials that come into direct contact with blood. More research in the area of tissue engineering is needed to address this problem. A program beginning this fiscal year is aimed at using genetic techniques to enhance the biocompatibility of cardiovascular implants. It is expected that various recombinant DNA and monoclonal antibody techniques will be applied during these studies.

MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Lenfant: During fiscal year 1993, NHLBI awards totalling approximately $32 million were made to minority institutions.

Mr. Stokes: Minority Institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Institute's programs and activities.

Dr. Lenfant: To remedy the situation you have described, the NHLBI has increased its outreach and technical assistance efforts to HBCUs. Some immediate successes have already been realized. For example, the number of minority schools receiving Minority Institutional Research Training awards nearly doubled within the past three years. In addition, all of the minority medical schools have received Preventive Cardiology Academic Awards, after the program was in existence for over 15 years without any awards going to these institutions.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research and research training.

Dr. Lenfant: The Institute supports an array of research training and career development programs for minority individuals at all levels of training and experience. Among them are: Research Supplements for Underrepresented Minorities, Adopt a School, Minority Access to Research Careers (MARC) Summer Research Training Program, Minority Predoctoral Fellowships, Minority Biomedical Research Support (MBRS), Minority School Faculty Development Award, Minority Institutional Research Training, Short-Term Training for Minority Studies, and the Research Development Award for Minority Faculty. The primary objectives of each of these programs are to identify, recruit, and train minority individuals for research careers in biomedical and behavioral sciences.

The Institute has a strong commitment to providing support to Research Supplements for Underrepresented Minorities. In FY 1994, 150 supplements were provided for a total of $6,273,000; in FY 1994 we expect to support 183 supplements for $7,979,000, an increase of 27%. Proposed funding for FY 1995 would provide $8,606,000 for 195 supplements, an increase of 8% over FY 1994.

The Minority Biomedical Research Support program is expected to receive a 4% increase in FY 1995 (from $2,647,000 in FY 1994 to $2,753,000 in FY 1995).

HEMOPHILIA RESEARCH

Mr. Hoyer: I am pleased to learn that the NHLBI recently issued an RFA for gene therapy research in hemophilia. Would you please describe the scope of this activity?

Dr. Lenfant: The purpose of this Request For Applications (RFA) is to support research that will lead to the successful application of gene therapy for hemophilia A and B. Research on effective gene therapy delivery systems, expression of the missing blood coagulation proteins, and initial testing of systems in animal models are expected to be supported by this initiative.

Mr. Hoyer: Would you please tell us how much funding has been assigned to this activity?

Dr. Lenfant: The projected funding for this RFA is $2 million in the first year with a total of $ 10.8 million for the five years of the program.

Mr. Hoyer: Would you please share with the committee your FY 95 plans to expand extramural research for Hemophilia Gene Therapy?

Dr. Lenfant: The institute will fund a Request for Applications (RFA) for Gene Therapies for Hemophilias A and B in FY 1994 in the amount of $2,000,000. This research program will continue in FY 1995.

Mr. Hoyer: What additional funding is proposed in FY 95?

Dr. Lenfant: This RFA will continue for 5 years with a FY 1995 budget of $2,080,000.

Mr. Hoyer: In 1992, NHLBI organized an intramural gene therapy for hemophilia project at NHLBI. Pleae give us an update on the progress that you have made over the last two years in your intramural research program in hemophilia gene therapy?

Dr. Lenfant: Hemophilia A and B, the major forms of hemophilia, are due to deficiencies in Factor VIII and Factor IX, respectively, which are principal components of the clotting system. Retroviral vectors have been constructed that express human factor IX and a modified form of human factor VIII. The Factor IX gene construct has been modified in four different ways in an effort to optimize the expression of Factor IX in different tissues.

Two different systems are under study for the production of Factor IX by gene treated cells. One involves the growth of Factor IX transformed cells in cell culture in a chamber with semi-permeable membranes. These membranes will allow the Factor IX that is produced by the cells to pass through and be collected while the cells are retained within the chamber and continue to produce Factor IX. In this way, quantities of Factor IX might be produced for therapeutic purposes. The other approach is to develop the procedures for expressing Factor IX in transformed cells in bone marrow grafts in situ.

Mr. Hoyer: We understand that Dr. Richard Morgan and others who were heading up the intramural gene therapy project have since left NHLBI to join the human genome project elsewhere at NIH - what is the impact of these moves?

Dr. Lenfant: Dr. Morgan is the only scientist engaged in hemophilia gene therapy who has moved from NHLBI to the National Center for Human Genome Research (NCHGR). Dr. Brian Safer, Acting Chief of the Molecular Hematology Branch and an internationally recognized expert in molecular biology is now devoting approximately 50% of his time and that of his associates to hemophilia gene therapy. His research efforts are enhanced by a CRADA with Genetic Therapy Inc. which includes the full time activities of one of their scientists. In addition, Dr. Safer continues to collaborate with Dr. Morgan in NCHGR. Also, the NHLBI non-human primate facility, and its staff, will be utilized by Dr. Morgan as well as by Dr. Safer when their studies reach that stage, and the clinical facilities of the NHLBI Hematology Branch are likely to be used by both groups when patient studies begin.

Two other scientists involved in gene therapy research also moved to the NCHGR, one from the Clinical Hematology Branch and one from the Pulmonary Branch. The former continues to collaborate with scientists in the NHLBI Hematology Branch and will also use the NHLBI non-human primate facility. Senior scientists in the Cardiology, Molecular Diseases and Hematology Branches are increasingly active in gene therapy research as applied to a number of cardiovascular diseases including restenosis following angioplasty, atherosclerosis, and genetic defects in hemoglobin synthesis. Approval has already been obtained for a clinical protocol for gene therapy of Gaucher's Disease which will be conducted in collaboration with scientists in the National Institute for Neurological Diseases and Stroke. Gene therapy continues to be a major component of the intramural clinical research program of NHLBI.

Mr. Hoyer: Have senior scientific personnel been identified to replace those who have transferred out?

Dr. Lenfant: Because of the relatively high salaries commanded by senior scientists, the great demand for such individuals, and the desire to expand new, imaginative approaches to gene therapy, the decision was made to recruit outstanding junior scientists into available positions in the Molecular Hematology Branch. Approximately 8 outstanding individuals, selected from many applicants, are now being interviewed for these positions. At this time, the FTE-freeze makes it impossible to hire from outside of the NIH and our selection may necessarily be limited to the candidates from within the NIH.

Several outstanding candidates have been identified for the position of Chief of the Pulmonary Branch. Several of these are engaged in, or would initiate at the NIH, research programs in gene therapy. In addition, as noted above, at least three other senior scientists in the intramural clinical branches are now actively engaged in gene therapy research.

Mr. Hoyer: Would you please summarize the focus of other research that's being conducted at NHLBI in relation to hemophilia, specifically related to: AIDS, hepatitis, liver disease, joint disease, inhibitors, prophylaxis.

Dr. Lenfant: The NHLBI intramural research program has one project on inhibitors that directly relates to hemophilia. The aim of this research is to understand the mechanism of inhibitor formation in hemophilia A so that inhibitor development can be prevented. Specifically, the study is targeted to determining the antigenic sites on the Factor VIII molecule and the reactivity of T cells to Factor VIII.

RESPIRATORY DISTRESS SYNDROME

Mr. Hoyer: Dr. Lenfant, the problem of neonatal respiratory distress syndrome has been substantially reduced due to surfactants. Is anything being done for adults suffering from respiratory distress syndrome?

Dr. Lenfant: Although the use of surfactant replacement for treatment of neonatal respiratory distress syndrome has greatly reduced mortality and resulted in significant cost savings, the application of this new treatment to adults with respiratory distress has just begun to be investigated. The Adult Respiratory Distress Syndrome (ARDS) is a very complex disorder and, unlike neonatal respiratory distress syndrome, the exact etiology and pathogenesis of ARDS are not well understood. However, bronchoalveolar lavage from adult patients with sepsis and early ARDS has shown biochemical and physiologic abnormalities of the surfactant. In addition, biopsies taken during the early phase of the disease show areas of air space collapse which indicate that the surfactant was deficient. These findings suggest that surfactants may indeed be beneficial to patients with ARDS. A small number of private sector-sponsored clinical trials have tested the efficacy of surfactants in patients with ARDS and shown mixed results. Clinical trials of different surfactants are being planned.

One particularly difficult problem is how to deliver adequate doses of surfactant to the affected regions of the lungs in adult patients. Another important goal for future research is to design more efficient and effective surfactant preparations. It is likely that abnormalities in lung surfactant are only part of the multiple problems affecting the lungs of patients with ARDS. However, there is optimism that treatment with surfactant will eventually help to ameliorate the lung injury and reduce mortality associated with this devastating lung disorder.

TUBERCULOSIS

Mr. Hoyer: As you know, the spread of Tuberculosis is one of this country's most urgent public health problems. What work is NHLBI doing in this area?

Dr. Lenfant: Tuberculosis (TB) rates have been increasing since the mid 1980s in association with the HIV epidemic and TB has become an increasingly serious public health problem. The Centers for Disease Control has forecast a worsening problem indicated by an increase in the actual number of cases in the U.S., particularly in minority populations.

Old methods of screening, diagnosis and treatment are far from optimal and more sensitive, faster and more specific ones are being sought. Lack of knowledge about the pathogenesis of TB, interactions between TB and HIV, molecular mechanisms associated with immunity, and emergence of drug resistant strains is hindering efforts to reverse the growing problem of TB. When TB was a common problem a generation ago, most physicians had experience treating the disease. However, with the decline of the disease, many physicians are not familiar with current TB control measures.

Three new TB initiatives were funded this year by the National Heart, Lung, and Blood Institute. Two of these, "Expression of TB in the Lung" and "Non-Immune Defense Against Tuberculosis in the Lung" now form a small basic research program. The projects in this program propose much needed research on the interaction of Mycobacterium tuberculosis with the lung. They will determine specific factors that influence host defenses. The investigators in this program will use powerful immunological and new molecular techniques to examine the way in which acquired factors, such as HIV infection increase the susceptibility of the lung to Mycobacterium tuberculosis and to look at the complex processes whereby cells in the lung interact with the tuberculosis organisms and how they interact with each other to prevent the spread of infection.

The third initiative, the Tuberculosis Academic Award Program is designed specifically to help medical schools improve the training of medical students and to reach out to practicing physicians to educate them in early diagnosis, treatment, and control methods. In addition, the Institute is developing a new program to encourage research on behavioral interventions for the control of TB. For example, we know that the future of TB control will require more effective adherence to treatment plans by patients and more collaboration among medical and nonmedical agencies in the community as well as improved public information and support of TB control programs. It is anticipated that this program will develop model programs that can be adapted at other sites in the country.

CYSTIC FIBROSIS

Mr. Hoyer: The first successful gene transfer for cystic fibrosis has just recently been reported. Please tell us about this effort and what it means for patients with this condition.

Dr. Lenfant: This development is a very significant one. In the experiment conducted within our intramural program at the NIH Clinical Center, four patients had normal genes transferred to the airway epithelium using a viral vector. The patients were three men and one woman age 23 to 25. One patient had an inflammatory response so the data were reviewed, and a decision was made to resume the protocol using a lower dose. All the patients are fine and are clinically stable.

The protocol is not designed to bring about clinical change in the patient. Rather, this study will provide information on safe dosage levels, the extent to which expression of healthy genes in the lungs occurs, and whether genes can be transferred on a repetitive basis without the body developing resistance and without the inflammatory side effects.

This research is in its early stages. It will be several years before larger clinical trials are possible. However, even if the technique is not feasible for cystic fibrosis, it may have therapeutic utility for other diseases where repetitive doses are not needed.

The Institute also supports extramural research on gene therapy for cystic fibrosis with a similar focus. In time, this promising research may lead to an effective therapy for cystic fibrosis patients.

ASTHMA

Mr. Hoyer: What can you tell us about recent progress in research aimed at understanding the processes that initiate, direct, and perpetuate the asthmatic response?

Dr. Lenfant: The asthmatic response is complex and diverse but there is now wide acceptance of asthma as an inflammatory process. Dissection of events which appear to initiate, direct, and perpetuate the development of the inflammation as well as the airway responsiveness that occurs in asthma is an area of active multidisciplinary research sponsored by the Institute. Understanding the events that lead to inflammation should help to develop new approaches to prevention and treatment of asthma.

Two cell types in the lung, the mast cell and the eosinophil, are thought to play a central role in promoting inflammation in asthma. Studies have revealed the critical role played by mast cells in the development of airways responsiveness. However, because the eosinophil is the predominant cell found in the airways in the asthmatic state, it is thought to be the "culprit" in human asthma. Techniques for the selective isolation and culture of pure populations of inflammatory cells, such as eosinophils, affords the opportunity to study mechanisms that underlie their selective migration to the airways in the asthmatic state. New insights into the complexity of asthma indicate that both altered neural activity in the airways, as well as airways inflammation, may be interrelated as potential causes or contributors to asthma. These lines of research will continue with the funds available in the 1995 President's request.

Mr. Hoyer: Episodes of asthma, especially when severe or frequent, can seriously affect a child's performance in school. Does NHLBI support any school-based programs to deal with this problem?

Dr. Lenfant: The Institute supports several school-based programs to help assure that children with asthma participate fully in all school activities and thus achieve their optimal school performance. In 1994 the NHLBI initiated a new research program that will develop and evaluate several different models for comprehensive school programs for asthma management and prevention. The results will be practical models for helping children with asthma perform well in school that will be applicable to school systems around the country. In evaluating new drug therapies for asthma, it is also important that children's school performance be assessed as an outcome measure. For this reason, children's intellectual and cognitive growth and development are being carefully measured in the Childhood Asthma Management Program, a clinical trial sponsored by the Institute to evaluate the long term effects of two types of anti-inflammatory asthma therapy.

The NHLBI's National Asthma Education and Prevention Program has developed a written guide for school personnel introducing them to actions they can take to make the school environment supportive for children with asthma. This program has been developed in cooperation with the U.S. Department of Education. The program has also produced an asthma awareness curriculum for the general elementary school classroom as well as a video and written materials on physical activity and asthma to help teachers and classmates learn how they can help a student with asthma. Through research funds, the NHLBI has supported development and evaluation of a program "Open Airways at School" to teach asthma management skills to children with asthma in the school setting. This program improved overall asthma management, reduced frequency and severity of episodes, and improved school performance. The results of this program are being disseminated widely. For example, the American Lung Association has adopted it as its flagship program for national distribution. Recently, the ALA has developed a partnership with the Zeta Phi Beta sorority, a national African-American professional women's organization, to implement the program in inner cities with the cooperation of the Indoor Air Division of the Environmental Protection Agency and the NHLBI's National Asthma Education and Prevention Program.

Ms. Pelosi: In your testimony, you mention the Working Group on Gene Therapy Approaches. It is my understanding that gene therapy has great potential for treatment of cancer and immune dysfunction. To what extent are the activities of the Working Group coordinated with other work going on in other Institutes? Is there an Inter-Agency Working Group or an NIH strategic planning process for setting a gene therapy agenda?

Dr. Lenfant: The NHLBI Working Group on Gene Therapy Approaches and Resources for Heart, Lung, and Blood Diseases was convened in 1992 to identify new research opportunities and chart a course for future NHLBI research efforts in this promising area. Thus, its main concern was development of a strategic plan for the NHLBI, not for the NIH as a whole. Similar activities are under way in other NIH components. Currently, the National Center for Human Genome Research plays an interdisciplinary coordination role within intramural research through an NIH focus group on human genetics.

The field of gene therapy is still in its infancy, but it is clear that increasing knowledge and activity in this area will reveal issues that provide opportunities for coordination across the NIH. For example, the National Center for Research Resources, in conjunction with the NHLBI and other NIH components, is considering development of an NIH-wide solicitation to develop vectors for gene therapy.

WOMEN AND CARDIOVASCULAR DISEASES

Ms. Lowey: About 1 in 3 American women suffers from some form of cardiovascular diseases. I am disturbed about reports citing that women frequently receive less aggressive care for heart ailments than men. Are women's hearts different and what research is the National Heart, Lung, and Blood Institute doing in this area?

Dr. Lenfant: Gender differences in the clinical presentation and outcomes of patients afflicted with heart disease have only recently been recognized and are poorly understood. For example, although women generally suffer a heart attack on average 9 years later than men, the initial heart attack is more often fatal. On the other hand, anginal chest pain, a key symptom that raises a suspicion of heart disease, is very common in women. However, in women chest pain does not correlate with obstructive lesions seen on coronary x-rays (angiograms) as well as it does in men.

It is not clear whether differences in care are due to gender bias or differences in clinical conditions. In point of fact, two recent articles: "Absence of Sex Bias in the Referral of Patients for Cardiac Catheterization" in the New England Journal of Medicine and "Chest Pain in Women: Clinical, Investigative and Prognostic Features," in the British Journal of Medicine, suggest that there is no gender bias. Nevertheless, gender differences in presentation and outcome in heart disease underscore the need for gender-specific research to optimize prevention, diagnosis and treatment.

The cardiovascular health of women is a priority for this Institute. The potential importance of the influence of gender is under-investigated. Through Institute-supported conferences, targeted research programs and investigator-initiated grants, the data base for understanding the role of gender is improving. For, example the Progesterone/Estrogen in Postmenopausal Women Intervention (PEPI) Trial will provide essential information on short term effects of estrogen and various estrogen/progesterone post menopausal hormone replacement therapies. Both basic science and clinical investigations to evaluate the physiologic influence of estrogen on the cardiovascular system, glucose tolerance (diabetes), serum lipids, and atherosclerosis will be addressed in a group of projects funded in response to an Institute-wide program, Collaborative Projects on Women's Health. Finally, the Institute just recently published a solicitation, "Evaluation of Ischemic Heart Disease in Women" which proposes to fund clinical studies to improve the reliability of cardiovascular testing in women. Optimal treatment for women afflicted with heart disease will require a sustained research effort and the Institute intends to support, lead and coordinate this effort.

Ms. Lowey: I have read that conventional methods for treating and diagnosing heart ailments are often not appropriate for women, in part because many women seeking treatment are older and sicker than their male counterparts. What progress are you making in helping devise alternative methods for diagnosing and treating heart ailments in women that can accommodate their differing needs?

Dr. Lenfant: Although gender differences in clinical presentation and outcome for heart disease have been documented their significance remains uncertain. For example, diagnostic testing in women suspected of ischemic heart disease is less reliable than in men. The poorer clinical utility of testing may discourage some physicians from even evaluating women with complaints which are potentially of cardiovascular origin. Precision in diagnosis is essential in order to optimally recognize and treat disease. Therefore the Institute has solicited a contract program entitled, "Evaluation of Ischemic Heart Disease in Women". This program encourages clinical studies to improve the reliability of cardiovascular testing for women suspected of heart disease. Secondary objectives of this program include improved understanding of chest pain in women.

Ms. Lowey: I have been actively involved in seeking to expand training programs for doctors that will help sensitize them to the physiological and other differences between men and women. Do you believe that better training for doctors in women's health can improve the quality of care received by women?

Dr. Lenfant: Yes, several reports show that both women and men benefit when receiving care by physicians of the same sex and/or physicians who specialize in a gender-specific medical specialty such as gynecology. The gynecologist and female general internist are more likely to routinely complete more thorough evaluations of women including screening for cancer and cardiovascular diseases. Thus, better training in health related gender differences is likely to improve quality of care.

Ms. Lowey: What is the National Heart, Lung, and Blood Institute doing to support training of this kind?

Dr. Lenfant: As research findings which affect recognition or treatment of cardiovascular disease become available the Institute employs several mechanisms to disseminate this information. These include medical journals, conferences, and public education programs, to inform the research community, practicing physician and the general public. Our national education programs, such as the National Heart Attack Alert Program, the National High Blood Pressure Education Program, and the National

Cholesterol Education Program specifically address women in their recommendations. Through its training grants, the Institute supports and encourages the training of women in cardiology fellowships and cardiovascular academic careers.

BIONUTRITION RESEARCH

Ms. Lowey: The budget justification refers to the Institute's preparation of an Action Plan for Bionutrition Research. Can you describe the main elements of this plan and your goals for its implementation?

Dr. Lenfant: The Institute's Bionutrition Agenda for the Year 2000 is a six-year plan that focuses on moving nutrition-related research forward through biotechnology. The Agenda consists of four sections: a research program; a training and career development program; a public education and technology transfer program; and a program organization component. The goals for the NHLBI Bionutrition Agenda are: to expand the science base that underlies our knowledge of human nutrition and its relationship to diseases of the heart, lung, and blood; to increase knowledge of nutritional interventions to prevent, cure, mitigate or interrupt the progression of nutrition-related components of heart, lung, and diseases; to use validated clinical information in our nutrition education programs; and to establish a Bionutrition Steering Group as a focal point for training, research and institutional collaborations. A variety of mechanisms will be employed to implement the program.

TUBERCULOSIS

Ms. Lowey: The Institute made six awards in FY 1993 under the TB Academic Award Program aimed at stimulating improvements in medical education and community response to this serious problem. Can you briefly describe these awards and tell us how you think they will contribute to addressing this urgent problem?

Dr. Lenfant: Despite major advances in our ability to diagnose, treat, and prevent this communicable disease, tuberculosis (TB) is spreading in the United States, due in part to inadequate education of health professionals, patients, and their families and the community. The Tuberculosis Academic Award Program is designed to assist medical schools to develop high quality curricula in teaching medical students the current principles and practices of preventing, diagnosing, managing, and controlling TB. In addition, this program will contribute to updating the knowledge and skills of practicing physicians and other health care workers in the community and will encourage collaboration with other community organizations to control TB in areas with a high incidence of the disease. A major objective is also to increase the awareness of health care providers of the unique ethnic, cultural, socioeconomic, and medical dimensions of TB.

The six medical schools that are currently receiving funds for five years are in areas serving minority and other high risk populations. Some of the innovative approaches being developed include involving neighborhood health care workers in the education process; having medical students provide services in health clinics, neighborhood centers, homeless shelters, soup kitchens, and drug treatment centers; providing TB testing programs in nursing homes; and establishing a hot line for referrals or calls for telephone consultation.

NHLBI plans to fund a total of 21 medical institutions over the next five years. It is anticipated that curricula and educational materials and strategies developed in these programs will be made available to other medical schools throughout the country and that some effective community intervention strategies will be developed. This program should make a major contribution to physician education, which is a prerequisite to controlling tuberculosis.

HISPANIC HIRING AND PROMOTION

Mr. Serrano: First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Lenfant: The National Heart, Lung, and Blood Institute (NHLBI) has selected Hispanic hiring and promotion as a top priority in its Affirmative Employment Program (AEP) and Federal Equal Opportunity Recruitment Program (FEORP) Plans for Fiscal Year 1994. Realizing the urgency of increasing the number of Hispanics within the Institute's work force, the Institute is actively pursuing this initiative.

The staff have established and are continuing to establish networks with Hispanic professional and technical organizations, Hispanic Program Managers, and other individuals who have knowledge of Hispanic populations. The purpose of these networks are: to announce vacancies, to solicit nominations for applicants, and to create an awareness of the Institute's employment needs. Additionally, the Division of Intramural Research invites Hispanic scientists to apply for its postdoctoral training opportunities which are the initial opportunities for most tenure appointments as permanent research scientists.

The Institute is aware of the fact that the numbers of minorities, especially Hispanics, Blacks, and Native Americans, entering the scientific academic disciplines are still very small. Staff have also noticed that these groups continue to be underrepresented in the science and engineering fields. Despite these factors, NHLBI is committed to attracting, recruiting and hiring minority scientists in its work force. To achieve this commitment, staff has developed a Minority Biomedical Research Training Program (MBRTP). The Minority Biomedical Research Training Program will offer underrepresented undergraduate and graduate students an unparalleled opportunity to receive training in the basic sciences and clinical disciplines under the mentoring and preceptorship of NHLBI research scientists within the Division of Intramural Research.

To assist managers and supervisors with daily interpretation of the Institute's AEP and FEORP Plans requirements, a Human Resource Management Framework with an overall mission statement has been developed. While the NHLBI pursues its mission to improves the health and well being of the public, it will also pursue a fair and equal approach to human resource management that allows the Institute to attract, hire, retain, and develop a skilled, innovative and diverse work force. The progress of managers and supervisors as they strive to achieve this fair and equitable approach to human resource management will be monitored by several techniques. All managers and supervisors are required to annually document, through the use of their Equal Employment Opportunity (EEO) critical element, what they have done to attract, hire, promote, and develop minorities and women. All appointments to positions within the Institute that have been identified as priority recruitment positions for Hispanics, Blacks, Native Americans, and women go through a strict advertisement method and approval procedure. Periodic reports are presented to staff relative to meeting the Institute's AEP and FEORP objectives. Finally, in order to ascertain the needs and plans for the management of the Divisions and Offices, annual personnel reviews are conducted with each Division and Office Director.

Mr. Serrano: What percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Lenfant: Approximately 1.3% of the Institutes budget is directed specifically at Hispanic Health Issues. Some of NHLBI's supported Hispanic Health Research includes:

Genetics of Atherosclerosis in Mexican Americans
Diabetes and Cardiovascular Risk in Mexico City
Survival After Myocardial Infarction in a Biethnic Texas Community
Hispanic Heart Healthy Milk Program
Unidos EN Salud -- Weight Loss for Mexican Americans
A Self-Management Educational Program for Hispanic Asthma
Intervention for Hispanic Children with Asthma

Mr. Serrano: What programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Lenfant: In addition to the numerous research training and career development programs of the Institute available to all individuals, the NHLBI also supports several minority-specific programs designed to increased participation of Hispanics in biomedical research. Two programs, the Research Development Award for Minority Faculty and the Research Supplements for Underrepresented Minorities, support significant numbers of Hispanics. Nine awards were made in FY 1994 under the Research Development Award for Minority Faculty program. Four of the awards, which provide up to five years of protected research support, were made to Hispanic investigators. Forty-eight of the 150 minority supplements awarded in FY 1993 were made to Hispanic individuals. In addition, significant numbers of Hispanic undergraduate and graduate students are supported through the Short-Term Training for Minority Students Program, which provides research opportunities for minority students in laboratories at major universities.

The Institute is a supporter of the annual meetings of the Society for the Advancement of Chicanos and Native Americans in Science, the National Association for Equal Opportunity in Higher Education, and the Association of Minority Health Professions Schools meetings. One-half day of each meeting is set aside for Hispanic and other minority high school students to visit with the conference staff and exhibitors to learn about programs available to support biomedical research careers. Additionally, the NHLBI has "adopted" a local intermediate school and a high school. Through this partnership program, students are exposed to NHLBI scientists and some have the opportunity to work in Institute's intramural laboratories to gain first-hand research experience.

Mr. Serrano: What is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Lenfant: The Institute is committed to ensuring appropriate representation of members of minority groups, including Hispanics, in the patient populations recruited for clinical trials. A variety of approaches are used to achieve this objective with respect to Hispanic participants. For multicenter trials, special attention is given to including study centers that have access to many Hispanic patients and demonstrated expertise in working with the Hispanic community. One example is the Child and Adolescent Trial for Cardiovascular Health, which includes two study centers that have successfully recruited large numbers of Hispanic children. Educational materials and a questionnaire sent home to the parents are in Spanish, and the project teams include a Spanish-speaking interviewer for children who prefer to use that language. In another large study, which is evaluating the usefulness of digitalis in prolonging the lives of heart failure patients, a Spanish translator is available to communicate with the study center in Puerto Rico and any other center needing translation. The consent form, patient information handbook, and patient identification materials are all available in Spanish. In a third program, the Arterial Disease Multifactorial Intervention Trial, a Hispanic nurse was hired at one of the study centers and arrangements were made for a physician and nurse from that center to speak at a Hispanic church and at a clinic that serves a Hispanic population. In addition, a press release was translated into Spanish and read over a Hispanic radio station. These examples illustrate the types of approaches used to recruit and retain Hispanic participants in clinical trials.

The Institute also plays an active role in ensuring rapid translation of results of clinical trials and other research efforts to health care professionals, patients, and the general public. On the recommendation of the NHLBI Ad Hoc Committee on Minority Populations, which includes four Hispanic members, we are developing a Hispanic Initiative to enhance our ability to deliver health messages to the Hispanic community. During the initial pilot phase, Spanish versions of current NHLBI publications will be produced and community outreach programs will be developed and evaluated in the Washington, D.C., area. If successful, these approaches will be considered for dissemination on a national level.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Lenfant: Data recently tabulated by the Division of Research Grants, NIH, indicate that 45 of the 2,634 NHLBI competing research project grant applications that were reviewed in fiscal year 1993 had a Hispanic principal investigator. Five grants received funding, which represents a success rate of 9.8 percent as compared to the overall NHLBI success rate of 21.0 percent. The Institute plans to look more closely at the data to identify possible reasons for this disparity, and to increase the pool of Hispanic applicants. It is important to note that these data may not be complete since NIH does not require applicants to specify their ethnic or racial origin; the applicant can voluntarily provide this information at their discretion.

RESEARCH FUNDING PER DEATH

Mr. Bonilla: Using fiscal year 1993 statistics, could you provide the subcommittee with HHS research funding of dollars spent per death for stroke, heart disease, cancer, diabetes, and HIV/AIDS?

Dr. Lenfant: The HHS funding per death for stroke, heart disease, cancer, diabetes, and HIV/AIDS is based on the National Center for Health Statistics Provisional Vital Statistics Data as of August 1993. Comparison of these diseases, however, is not directly comparable since HIV/AIDS is a contagious disease whereas stroke, heart disease, cancer and diabetes are chronic diseases.

These data were prepared by the Office of the Assistant Secretary for Health.

	FY 1993 Research Spending ($000)	Number of Deaths	Funding Per Death
Stroke	$ 108,304	148,110	$ 731
Heart Disease	755,077	731,420	1,032
Cancer *	1,954,122	526,940	3,708
Diabetes	286,774	52,900	5,421
HIV/AIDS	1,284,496	39,940	36,763

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

RESEARCH COORDINATION

Mr. Smith: Now that the National Institute for Mental Health is firmly reestablished at NIH, how have you and that Institute worked out a division of labor in neurological research that avoids duplication?

Dr. Grady: NINDS and NIMH have a long history of mutual interests and collaborations predating the return of NIMH to NIH. Also predating NIMH's return are a number of standard research management practices designed to minimize duplication, ensure appropriate assignment of research programs, and provide opportunities for cooperation.

All grant applications are assigned to funding institutes and scientific review groups by the NIH Division of Research Grants. Occasionally applications are dually assigned so that one or more institutes will have the opportunity to fund, but this is a highly interactive process in which all potential participants are fully informed. Announcements of new programs are circulated to all institutes, which then have the opportunity to indicate an interest in cosponsoring the announcements or negotiate changes to eliminate program overlap. In addition to these formal mechanisms for coordination, both intramural and extramural staff have frequent opportunities for coordination through seminars, workshops, and research collaboration.

PARKINSON'S DISEASE CLINICAL TRIAL

Mr. Smith: Your fetal tissue transplant grant has generated controversy because its design requires that some of the patients undergo surgery to implant placebos. Why is it appropriate to put patients through brain surgery of no medical value?

Dr. Grady: There is no intent to implant placebos as part of this trial. This trial will include 40 participants, 20 of whom will receive fetal implants. The other 20 will go through the same preparation and post-operative followup but will not receive any implants. The trial is designed to minimize the likelihood of short-term changes being mistaken for longer lasting effects of an implant. Like the experimental group, the control group will have burr holes, not brain surgery, in which holes are drilled into the skull, but the dura mater, or brain covering, will not be penetrated. They will not receive implants, nor will there be any surgery to the brain in the course of the study. Neither the patients nor the examining physicians will know whether the patients received the burr holes or the full implant procedure. This will be explained beforehand as part of the process of recruitment for the study and informed consent will be obtained. Those participants will also be informed that they will have the option of receiving implants at a later time if the procedure is shown to be beneficial.

The burr hole procedure is used for other conditions--such as injury, stroke, or meningitis--in which it is necessary to administer drugs, monitor intracranial pressure or perform other procedures. Burr holes carry negligible risks and are frequently done as a preliminary or preparative stage for subsequent surgery or other procedure. The risk of burr holes alone are thought to be entirely acceptable in view of potential benefits and knowledge to be gained from this controlled study. Like all research involving human subjects, this proposal was reviewed and approved by the Institutional Review Boards of the three collaborating institutions as well as NINDS advisors and staff.

INTRAMURAL STAFFING

Mr. Smith: According to your budget justification, your intramural research staffing increases from 1993 to 1994 and then drops back down in 1995. What is happening here?

Dr. Grady: In the budget justification, the number of intramural research Full Time Equivalent (FTEs) reported for FY 1993 represent actual usage, where as for FY 1994 and 1995 the staffing amounts reflect FTE ceiling levels. This causes what appears to be an increase then decrease in staffing levels. In FY 1993 the intramural research program was 30 below its authorized ceiling. Comparable ceiling levels of intramural research FTEs for FY 1993, 1994 and 1995 are 534, 521 and 503 respectively. This shows a steady decline in the number of FTEs.

AVERAGE COST OF GRANTS

Mr. Smith: Despite the expensive equipment needs of neurological research, the average cost of your grants is lower than a number of Institutes. What accounts for this lower cost?

Dr. Grady: NINDS maintains a higher proportion of its research project grant (RPG) portfolio in individual investigator initiated projects (R01, R29) than the NIH average. Since these mechanisms have lower average costs than multi-project grants, the overall average cost is lower for NINDS. In addition, as a cost containment measure, in 1991 NINDS placed a direct cost cap of $750,000 on multi-project grants, which has further reduced the average RPG cost.

SUPRANUCLEAR PALSY

Mr. Smith: Last year's House report asked you to be prepared to discuss research on supranuclear palsy at this year's hearing and to describe the best mechanisms to move this field forward. What can you tell us in this regard?

Dr. Grady: Characteristic symptoms of progressive supranuclear palsy (PSP) are similar to Parkinson's disease (PD), but different enough to distinguish PSP from PD. NINDS efforts to move the PSP field forward have included a study of the prevalence and natural history of PSP and a program announcement on movement disorders that specifically included PSP. In November, 1993, the NINDS sponsored a workshop to assess the reliability of neuropathological diagnosis in PSP. A case controlled clinical study, which complements the workshop, is examining the accuracy of diagnosis of PSP in clinical centers. The results of the study will be published in 1994. In addition, intramural efforts include studies to characterize the cognitive and motor aspects of patients with PSP. NINDS research emphasizes efforts to understand the neurochemical impairment in PSP and how it might differ from that seen in PD. Such efforts will provide necessary information and insights needed to identify methods of treatment.

SYRINGOMYELIA

Mr. Smith: The Committee heard about the disease of syringomyelia last year for the first time. Can you tell us more about this disease and the state of research?

Dr. Grady: Syringomyelia is a chronic progressive disease of the spinal cord characterized by cavitation of the cord. The cavities fill with fluid. The disease is associated with sensory loss, pain, and in some cases weakness of the limbs. Specific treatments, which may include surgery and shunts to control the fluid, vary from patient to patient according to the cause and extent of the lesion.

NINDS research efforts on syringomyelia include studies of trauma, developmental abnormalities, and neurosurgical approaches. NINDS intramural efforts include studies of the dynamics of cerebrospinal fluid in patients with syringomyelia as well as new surgical techniques.

NINDS is organizing a workshop to summarize the state of knowledge and identify the research questions and opportunities that need to be addressed to advance understanding and treatment of syringomyelia. The workshop is scheduled for June 20 and 21 of this year. A lay summary will be prepared for patient use, in addition to the scientific summary of the conference.

MOVEMENT DISORDERS

Mr. Smith: Some in the disease community are lobbying for the creation of research centers on rare movement disorders. Are centers an appropriate mechanism for such research? With the current budget constraints, is this a high priority use of your funding?

Dr. Grady: Research centers can provide a favorable environment for studying difficult research questions becuase they facilitate collaboration between basic and clinical investigators. However, the rarer types of movement disorders are sufficiently uncommon that single centers might not be able to acquire enough patients for useful study. Availability of promising research approaches is critical to the advancement of a new field. Given the lack of promising leads, limited response to earlier program announcements and budgetary constraints, the FY 1995 budget proposal does not include funding for research centers on movement disorders. A small number of pilot centers for the study of movement disorders could play a significant role in accomplishing research goals. However, centers represent only one approach to stimulating the interest of the research community to seek out and pursue opportunities in research on rare movement disorders. Other options include solicitation of investigator-initiated research, either as freestanding projects or supplements to ongoing grants in closely related areas such as Parkinson's disease, and research workshops.

DISEASE FUNDING

Mr. Smith: Identify projected 1993-1995 spending on the following: Gaucher's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis, head injury, stroke, epilepsy, Batten disease, neurofibromatosis, dystonia, post-polio syndrome, spinal cord injury, narcolepsy, syringomyelia, supranuclear palsy, and Parkinson's disease.

Dr. Grady: The information follows:

(Dollars in Thousands)

Disease/Disorder	FY 1993 Actual	FY 1994 Estimate	FY 1995 Estimate
Gaucher's Disease	$7,531	$7,599	$7,717
Alzheimer's Disease	42,266	44,464	46,091
Huntington's Disease	42,250	44,010	45,567
Multiple Sclerosis	53,328	55,494	57,272
Head Injury	29,235	32,977	34,302
Stroke	67,050	70,815	73,576
Epilepsy	48,083	50,700	52,665
Batten Disease	2,993	3,138	3,260
Neurofibromatosis	5,260	5,507	5,718
Dystonia	4,050	4,143	4,238
Post-Polio Syndrome	1,239	1,227	1,227
Spinal Cord Injury	16,697	18,063	18,729
Narcolepsy	3,130	3,276	3,407
Syringomyelia	486	498	509
Supranuclear Palsy	a/	a/	a/
Parkinson's Disease	44,978	46,730	48,454

a/ Funding for Supranuclear Palsy is included in Parkinson's Disease Research.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject matter of research centers supported in 1994.

Dr. Grady: The NINDS has included in its FY 1994 estimate support for 46 Research Centers. Of this number, 11 will be Exploratory Grants (P20) and 35 will be Specialized Centers (P50) and are broken down by subject area as follows:

Subject Area	P20	P50	Total
Neurological Disorders of Early Life	--	1	1
Neurological Disorders of Aging			
Parkinson's	--	1	1
Alzheimer's Disease	--	2	2
Stroke	--	6	6
Epilepsy	--	4	4
Sleep Disorders	--	1	1
Demyelinating or Sclerosing Disorders			
Multiple Sclerosis	--	4	4
Amyotrophic Lateral Sclerosis	--	1	1
Neuromuscular Disorders	--	1	1
Trauma and Injury			
Head and Brain Injury	--	8	8
Spinal Cord Injury	--	3	3
Neonatal Brain Injury	4	--	4
Brain Tumors	7	2	9
Positron Emission Tomography	--	1	1
	11	35	46

SLEEP RESEARCH

Mr. Smith: The National Institute of Neurological Disorders and Stroke is the major National Institutes of Health Institute which focuses on the study of Narcolepsy. Can you describe NINDS' programs in Narcolepsy research?

Dr. Grady: Narcolepsy is a neurological condition characterized by irresistible episodes of sleep. NINDS research includes studies devoted to the discovery of the genetic origins of narcolepsy as well as various other sleep disorders, the search for more effective medications for those afflicted, and the neurochemical mechanisms of narcolepsy. While studies in the naturally occurring narcoleptic canine model suggest an autosomal recessive mode of transmission, research is needed to clarify the genetic mechanisms involved in patients with narcolepsy. NINDS supports an ongoing study to address this question.

Mr. Smith: The establishment of the National Center for Sleep Disorders Research was established to help coordinate sleep disorders research throughout NIH, but not to replace existing research being conducted at any Institute. Will funding for Narcolepsy research at NIH still receive the high priority it has had in the past?

Dr. Grady: Narcolepsy research remains a priority for NINDS. In 1993, NINDS and the National Institute of Mental Health co-sponsored a program announcement to encourage new research studies in both basic and clinical aspects of narcolepsy. Examples of areas of potential research included studies on the pathophysiology of narcolepsy, abnormalities of circadian rhythms, the genetics of narcolepsy, and the development of new therapies.

Mr. Smith: Can NINDS work with the new Center to establish collaborative initiatives in areas of common interest?

Dr. Grady: For the last eight years, the NIH Institutes comprising the Trans-NIH Sleep Research Coordinating Committee, have utilized this Committee to coordinate their sleep research activities by both formal and informal exchanges, including periodic meetings, issuance of joint program announcements, and sponsorship of public meetings. The NINDS looks forward to working with the Committee, now attached to the Center, to continue the collaborative and coordinated sleep related activities of the member institutes.

Mr. Smith: What is the status of accomplishments for sleep research and the maintenance of narcolepsy research using animal models?

Dr. Grady: Current research activity on the neurobiology of sleep is diverse. Examples include investigations of the neuronal activity associated with abrupt changes in the electrical activity of the brain during transitions from slow wave to rapid eye movement sleep, of the immune system interaction with different sleep stages, and of genetic abnormalities on chromosome 14 associated with narcolepsy. This locus on chromosome 14 is also known to be the locus of abnormalities found in autoimmune disorders.

MOVEMENT DISORDERS

The NINDS uses the research grant mechanism to provide support for maintenance of a variety of animal models of human disease, including narcolepsy.

Mr. Smith: Please describe for the Committee your plans for increasing extramural research in the category of illness referred to as "movement disorders".

Dr. Grady: Advancing our understanding and improving the treatment of movement disorders is a high priority of our Institute. NINDS held a workshop on dystonia in February, 1993 and another on neuropathological diagnosis in progressive supranuclear palsy (PSP) in November, 1993. Publications from those meetings are expected to stimulate additional interest and research activity concerning movement disorders. NINDS issued a program announcement in 1991 to encourage new studies in movement disorders and continues to receive applications for research support. NINDS also issued a program announcement in February, 1994 to encourage new studies on neurogenetic disorders of infancy and childhood including movement disorders.

RARE DISORDERS

Mr. Smith: Now describe for us your plans for increasing extramural neurological research in the "rare disorders".

Dr. Grady: NINDS research focused principally at the basic biological and molecular level yields advancement in knowledge of rare diseases that may be transferred to clinical application and may have relevance to many other neurological disorders. NINDS actively encourages new and more varied research in rare disorders by issuing program announcements and requests for announcements to stimulate investigator interest, and organizing and conducting various workshops. A few examples include: issuance of program announcements on Duchenne's muscular dystrophy and neurogenetic disorders; organization of a workshop to elucidate research questions and opportunities to advance understanding and treatment of syringomyelia; and issuance of a joint RFA with NIDDK to explore new methods of gene therapy for genetic metabolic diseases, such as Batten disease.

NUMBER OF GRANTS FUNDED

Mr. Porter: According to Page 56 of the budget justification, under the 1995 budget, the total number of grants funded by NINDS would decline from 2,062 to 1,951. This decline will occur despite a large increase in new grants. Why will the total number of grants decline, and what is the impact of this reduction on your Institute?

Dr. Grady: The decline in total number of grants funded is directly related to the research project grant (RPG) mechanism. The total number of RPGs drops from 1,764 to 1,652 between FY 1994 and FY 1995. There are two factors responsible for this decline. Although the overall funding for RPGs increases 3.53 percent between FY 1994 and FY 1995, the average cost of grants increases approximately 10 percent. Between FY 1994 and FY 1995, the average cost of non-competing grants increases over 13 percent due to the increased average cost of the FY 1994 competing grants entering the FY 1995 non-competing category, and the average cost of new and competing grants increases 4.1 percent. Because of this, fewer grants can be supported. The decline in noncompeting continuation grants that results in the large number of new and competing grants in the FY 1995 budget justification is due to grant cycling. This year a larger than normal number of noncompeting RPGs are entering into the competitive renewal process. The reduction of RPGs will significantly impact on the rate at which the institute can pursue its research goals.

Mr. Porter: Please place a chart in the record which shows the number of total grants funded by NINDS over the last five years broken out by AIDS and non-AIDS.

Dr. Grady: The information follows:

NINDS Research Grants Funded

Fiscal Year	AIDS	NON-AIDS	Total
1990 Actual	34	2,002	2,036
1991 Actual	36	2,073	2,109
1992 Actual	37	2,048	2,085
1993 Actual	43	2,021	2,064
1994 Estimated	43	2,062	2,105
1995 Estimated	41	1,951	1,992

STROKE

Mr. Porter: You mentioned in your statement your efforts to prevent recurrent stroke. Why have you targeted this problem and what progress have you made?

Dr. Grady: Stroke causes death and disability because the blood supply to part of the brain has been disrupted. A person who has had a stroke and recovers is not "out of the woods" completely; that person is often still at risk for another stroke. Recurrent stroke increases the risk of death and disability.

Through research to understand risk factors for stroke and research to find new ways to prevent and treat stroke, we want to interrupt this chain of events. For example, NINDS supports a clinical trial to evaluate whether estrogen will prevent stroke in post menopausal women who have already had a nondisabling stroke. Another trial will examine the use of warfarin in recurrent stroke. The benefit of surgery to prevent stroke has been demonstrated in patients with severe blockage of the carotid artery who have already experienced symptoms of stroke.

Mr. Porter: Are you investigating stroke in infants?

Dr. Grady: Stroke, the third leading cause of death in the United States, can occur at any age. Premature infants are particularly susceptible to bleeding in the brain. The long-term consequences include mental retardation, seizures, and cerebral palsy.

NINDS has supported an important advance in preventing brain bleeding in very low birthweight babies. Results from the study show that babies treated within 6-12 hours of birth with a drug called indomethacin are less likely to have a hemorrhage, and when it does occur, it is less severe.

We need to learn more, though, about the many causes and consequences of brain hemorrhage in infants. For instance, there is evidence that newborns may experience phenomena similar to that which occurs in the adult brain after it is deprived of proper oxygen levels (hypoxia) or blood circulation (ischemia). As with adults, these dynamic processes, though damaging, also present an opportunity to intervene and protect brain cells and preserve brain function. However, research is needed to further define the specific mechanisms of damage in the neonatal brain, determine the impact on neurological function, and explore therapeutic strategies appropriate to the newborn. The recently established pilot research centers for neonatal brain injury will be an important part of this effort.

NEUROGENETICS

Mr. Stokes: Can you bring us up-to-date on the progress that has been made with respect to the genes associated with neurological diseases and disorders?

Dr. Grady: Major discoveries have been made over the past year in identifying genes associated with neurological disorders. The first gene for a neurodegenerative disorder of adult life was identified by NINDS-supported scientists; it is the gene for the familial form of amyotrophic lateral sclerosis (ALS), a motor neuron disease. The gene that was discovered produces an enzyme, superoxide dismutase (SOD), known to be involved in neutralizing the deleterious effects of free radicals. This discovery has encouraged further study of free radicals in ALS as well as other neurological disorders.

The ALS discovery was followed by the discovery of the gene for Huntington's disease (HD), a degenerative disorder of the brain that first affects the basal ganglia. Scientists found that people with HD have a three base sequence (CAG) on chromosome 4 that is replicated 40 or more times. The genetic mutation is similar to the type of defect responsible for fragile X syndrome, myotonic dystrophy, and spinobulbar muscular atrophy. Several months after the HD discovery, NINDS-supported scientists reported the same mechanism is responsible for another neurodegenerative disorder, spinocerebellar ataxia type I (SCA1). In SCA1, the CAG repeat is found on chromosome 6. Evidence suggests that in both diseases, a higher number of repeats correlates with earlier age of onset and rapid disease progression. This phenomenon, known as a triplet repeat, has drastically changed understanding of how diseases can be inherited and expressed.

Intramural scientists have narrowed the search for the gene that is mutated in patients with Type C Niemann-Pick disease to the long arm of chromosome 18. NINDS grantees identified the gene for neurofibromatosis 2 on chromosome 22. An important advance for tuberous sclerosis (TS) research was announcement that the gene for TS2 was identified on chromosome 16. NINDS grantees continue to search for the TS1 gene on chromosome 9. In addition, NINDS supports research on the physical map for chromosome 9 which will contribute to TS efforts.

INTRAMURAL PROGRAM

Mr. Stokes: Quite often we hear the comments, "why does the NIH need to have an intramural program isn't it just a duplication of research done extramurally, invest those funds in additional research project grants." Doctor, what is the case for an intramural program at your Institute?

Dr. Grady: The major strength of the NINDS intramural program and the source of its unique contributions to the understanding and treatment of brain disorders has been the investment in long term research and research studies that help to build a scientific base from which other studies could proceed. More than 600 disorders affect the nervous system including commonly known conditions such as stroke--the third leading cause of death, epilepsy, muscular dystrophy and multiple sclerosis as well as less well-known disorders such as Batten disease and neurofibromatosis. In an Institute with responsibility for such a wide range of diseases, the intramural program strategy has been especially productive in generating new knowledge of the basic structure and function of the nervous system, as well as infectious, chronic, and degenerative neurological disorders.

For example, multidisciplinary studies conducted by intramural scientists over the past thirty years in populations around the world account for much of the current level of understanding of slow viruses and related disorders. This work has resulted in important contributions to recent studies of HIV, HTLV-1, hanta virus, herpes virus, and other viral infections in this country. The earliest contributions from this Institute to the national neuro-AIDS research effort originated intramurally.

Intramural clinical studies often involve the development of leading edge technologies and treatments. Scientists in the NINDS intramural program have characterized the genetic defect responsible for Gaucher's disease and developed the first effective treatment for this disorder--a process that took more than 20 years to bring to fruition. Success with this treatment is pointing the way toward treatments for many similar lipid-storage diseases. At the same time, other approaches to treating Gaucher's disease are being explored.

Other innovative approaches undertaken by the intramural program include efforts to develop a visual prosthesis and potential new therapies for brain tumors.

Over the past four years, scientists have conducted extensive longitudinal studies of the natural history of relapsing-remitting multiple sclerosis (MS) using monthly magnetic resonance imaging (MRI) evaluations. The data derived from this study are the most extensive available and have important implications for understanding the natural history of MS.

Intramural research efforts to identify and characterize various subtypes of dopamine receptors have enlightened knowledge of the effects of L-dopa, the major drug for Parkinson's disease, and have provided new leads to develop more beneficial medications with fewer unwanted effects.

CLINICAL TRIALS

Mr. Stokes: What major clinical trials are underway at your institute and what improvements in the quality of life do they offer, elaborate.

Dr. Grady: We are in an era in which we are seeing the fruits of investments in basic research pay off with new strategies for prevention and treatment of neurological disorders ready for evaluation in clinical trials.

The NINDS currently supports a number of clinical trials of strategies to prevent or treat stroke. Through NINDS support of clinical trials, we have already demonstrated the benefits of surgical and medical approaches to prevent stroke in specific patient populations. In ongoing trials, we are addressing other risk factors and other populations to continue to make progress against this third largest killer in the U.S. The NINDS estrogen trial is an example of this effort. Women in the trial have already had a non-disabling stroke. We want to prevent a second stroke, because the risk of disability increases with subsequent strokes. In two other trials, we are evaluating the use of medications provided soon after the onset of a stroke to improve recovery.

A trial of tissue implants in Parkinson's disease will help us to answer important questions surrounding this approach and will contribute to the total research effort in Parkinson's disease involving basic science and clinical studies of other approaches to treatment.

The National Acute Spinal Cord Injury Study III is examining the use of tirilizad to foster recovery after spinal cord injury. One consequence of head injury can be the development of seizures. NINDS supports a clinical trial to evaluate the effectiveness of valproate to prevent post-traumatic seizures.

Intramural clinical trials, include the use of botulinum toxin for focal dystonias and new treatments for brain tumors, for which limited treatment strategies exist.

NINDS supports a clinical trial of bone marrow transplantation to prevent the progressive mental retardation and neurologic disability of seven neuronal storage diseases: three types of mucopolysaccharidoses (Hunter syndrome, Hurler syndrome, and Sanfilippo syndrome), metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy, and Gaucher type III. The approach is based on evidence that some cells in affected organs originate from bone marrow and are continuously replenished. Transplanted bone marrow provides a source for healthy cells that appear capable of correcting the metabolic disorder.

A clinical trial began during the past year on the pre-hospital treatment of status epilepticus, a life-threatening condition when a seizure persists uncontrolled for a long period of time. The trial will evaluate whether two treatments currently used in hospital emergency rooms for the treatment of status epilepticus are more effective when administered "in the field" by para-medical personnel before transportation of the patient to the hospital.

NEUROLOGICAL RESEARCH FOR CHILDREN

Mr. Stokes: How extensive is the problem of neurological diseases and disorders in children? What specific research is underway to address neurological diseases and disorders in children?

Dr. Grady: Neurological disorders can affect children from birth and throughout childhood, too often causing death and disability and limiting opportunities for education and employment. NINDS supports and conducts research efforts in epilepsy, learning disorders, cerebral palsy, autism and behavioral disorders, and neuromuscular disorders with importance for improving the health of children in the United States.

Many of the neurological disorders that affect children are genetic. NINDS grantees and scientists have identified the genes for many of these disorders and have made progress in understanding the disease process. This opens the way for better diagnosis and new treatment strategies. As an example, intramural scientists developed enzyme replacement therapy for Gaucher's disease and are planning gene therapy studies for these patients. We have taken steps to encourage new studies to develop gene therapy for inherited metabolic diseases and Duchenne muscular dystrophy.

In the area of neonatal brain injury--which might result, for instance, from complications of birth or premature birth--NINDS has recently funded new pilot research centers to encourage new understanding and new treatments. We fully expect to report advances from this effort over the next several years. NINDS recently announced an important advance in preventing brain bleeding in newborns. An NINDS-supported study has recently shown that very low birthweight babies treated with a drug called indomethacin--within 6-12 hours of birth--are less likely to have bleeding in the brain known as intraventricular hemorrhage (IVH). The study showed that when IVH does occur in treated patients, it is less severe, and therefore, less likely to cause permanent damage.

The NINDS also sponsored a workshop in 1993 on the consequences of traumatic brain injury (TBI) in children, at which future directions for research were identified. Traumatic injury is that which results from accidents or some other type of physical injury.

STROKE

Mr. Stokes: What specifically is the Institute doing to increase the understanding of stroke in minorities? In your professional judgment, what more needs to be done to increase this knowledge and advances, and what resources are needed to do it?

Dr. Grady: The question of stroke in minorities is a perplexing problem involving many complex interactions between the social and economic environment and intrinsically different responses in the biological system itself. We are moving to include a broader representation of the population in all of our clinical trials, which will help with our understanding of different responses to treatment; however, the NINDS has more fundamental questions to be answered that require the entire focus of the research to be on this important problem. For this reason, the NINDS has started several projects to answer some obvious but as yet unanswered questions. Are minorities having more strokes because they are more heavily exposed to risk factors than the majority, or are there intrinsically different responses to the same risk exposure? We have started several research projects to answer these questions. Pilot studies have raised some very interesting questions about the location of and extent of atherosclerosis and differences in blood coagulation that could explain the high stroke rate in minorities. Convincing answers and full understanding will require large clinical trials and hospital based epidemiological case-control studies. Proposals are already being submitted to answer these questions in response to previous initiatives by the NINDS.

Mr. Stokes: In total, in your professional judgment, how much is needed to support stroke research?

Dr. Grady: A funding level for stroke research of $95 million in FY 1995 would allow NINDS to pursue the opportunities in stroke research identified by the National Advisory Neurological Disorders and Stroke Council in its 1992 status report, Progress and Promise.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly. How much is included in the FY 1995 budget request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Grady: Many neurological disorders have a genetic cause, so the advances in neurogenetics offer great hope to millions of our citizens. The discovery of a gene and its functions allows us to focus efforts on genetic counselling and development of interventions to replace a missing or defective gene product.

Gene therapy--the actual alteration of the genetic material--is changing the treatment of neurological disorders in two important ways. First, if we can alter a disease gene to restore normal function, we can hope to cure the condition completely. An intramural trial of gene therapy for Gaucher's disease is planned for later in the year. In addition, NINDS and NIDDK have issued a joint Request for Applications for studies of gene therapy for inherited metabolic disorders including Gaucher's, Batten disease, and Niemann-Pick disease. Other targets of research interest include some of the inherited epilepsies, hereditary cerebellar ataxias, and Duchenne muscular dystrophy.

A second application of gene therapy is the use of altered genes to deliver new forms of treatment. This approach is being used in new treatments for brain tumor, a disorder that has been highly resistant to treatment because of the limitations of surgery and drug therapy posed by the brain's anatomy and the blood-brain barrier. In this trial, cells infected with a virus engineered to be sensitive to the drug ganciclovir are injected into brain tumors in order to provide a "target" for the drug. This innovative approach has the potential for application to other conditions and an additional study aimed at a different type of brain tumor is already being planned.

The FY 1995 budget would provide $3,435,000 for gene therapy research. Expenditures in FY 1993 were $3,291,000 and are estimated to be $3,361,000 for FY 1994. It should be noted, however, that the Institute's substantial investment in the broader field of genetic research provides the information necessary to proceed with applications of gene therapy. In the current fiscal year, for example, NINDS expects to spend $44,949,000 on gene mapping and sequencing and $8,139,000 on genetic engineering and recombinant DNA studies in addition to projects specifically dealing with gene therapy.

MINORITY HEALTH

Mr. Stokes: As the director of an Institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues -- while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and -- while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Grady: Improving the health of minority Americans is a high priority for NINDS, and we are pursuing that goal in several ways. The more we know about disease mechanisms and risk factors in specific populations, the better prepared we can be to identify methods of prevention, diagnosis, and treatment. For this reason, we are focusing on population differences in several studies of stroke risk factors, since we know that African American and Hispanic people bear a disproportionate share of the burden of stroke. Recent and expected advances in epilepsy and head and spinal cord injury will also improve the situation of minority Americans. The discouraging news, however, is that improvement in minority health has not been as rapid as one would expect, based on scientific advances. NINDS will continue to seek ways to narrow the gap between the health of majority and minority citizens--for example, through public and professional education materials.

While racial differences in risk factors and disease prevalence are clearly important, one's health is also dependent on access to preventive and treatment services as well as general economic wellbeing. For example, good prenatal care and adequate nutrition in early life are critical to the child's growth and ability to function, particularly in view of the nervous system's vulnerability to injury in early life. While we must continue our efforts to find answers through research, real improvement in minority health will also depend on the availability of health care and economic security for all our citizens.

BASIC RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising basic research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Grady: There are several exciting areas of opportunities to increase understanding of the brain and the nervous system and neurological disorders. Underlying many of the research opportunities in basic and clinical neurological research has been the development of non-invasive techniques such as NMR spectroscopy and near-infrared spectroscopy which have provided valuable information concerning the structure and function of the nervous system.

Neurodegenerative Disorders: Research on degenerative disorders of the brain is very exciting right now, as scientists are beginning to identify the different factors involved--genes, growth factors, receptors--in the death of nerve cells. Several neurological disorders are characterized by loss of function primarily in specific groups of nerve cells (e.g., substantia nigra in Parkinson's disease; basal nucleus cells in Alzheimer's disease; motor neurons in ALS; and basal ganglia cells in Huntington's disease). Advances in molecular genetics and neurochemistry have laid the foundations for progress in describing the cellular and biochemical abnormalities that underlie the selective vulnerability to these disorders. For instance, the finding that the familial ALS gene produces an enzyme that normally neutralizes the effects of free radicals has opened exciting new leads which will be pursued in research on ALS and other debilitating neurological disorders, possibly leading to new treatments.

Neural Growth and Regeneration: Several years ago investigators working in Europe showed that a chemical factor found in the white matter of the central nervous system inhibited new growth of nerve fibers. The finding that astrocytes reverse inhibition of regeneration by white matter was a pivotal discovery, demonstrating that regeneration and recovery from trauma depended on both stimulation of new growth and on an absence of inhibition of that growth. Strategies to overcome an unsupportive environment within the injured brain and spinal cord are underway on several fronts. One approach is to allow the natural, positive (growth-supporting) portions of the environment within the nervous system to influence the negative (growth-inhibiting) portions of that environment. Investigators used in vitro techniques to grow hippocampal neurons (brain cells important in memory functions that are often damaged in traumatic brain injury) on frozen slices of brain. Small nerve processes grew on areas of gray matter, but not on white matter. If conditioned medium, containing factors produced by a support cell of the brain, the astrocyte, was added, neurites extended onto the white matter. This very fundamental work clearly shows that the cellular and chemical environment or the brain is crucial for successful regeneration, and that an unfavorable milieu is not permanent but can be influenced by natural processes. This work is important to related studies of growth factors and implantation, which also seek to re-establish an environment that would allow directed axonal growth, reconnection of neural circuits, and functional return.

Continued research on the plasticity of the neuronal environment is relevant to any disorder that involves neuronal death or deformation of circuitry: trauma to the central nervous system, stroke, degenerative disorders, mental illness, and seizures, to name only a few.

Secondary Damage: Not all damage to the nervous system occurs at the moment of mechanical injury. Much of the permanent and functionally relevant damage is secondary, the result of a cascade of cellular events set in motion by the initial insult. One type of secondary injury that can be controlled is traumatically induced vascular damage in head injury. Interruption of the blood supply produces ischemic damage to the nervous tissues layered upon any mechanical trauma that may have occurred. Oxygen radicals, produced in the endothelium of affected blood vessels, result in breakdown of the blood brain barrier and disruption of the delicate internal milieu of the brain. Anti-oxidant drugs reduce vascular sequelae and result in improved recovery. This applied research is a good example of "bench to bedside" therapy: clinical work on methylprednisolone and a compound abbreviated as "PEG-SOD" resulted from laboratory data.

The returns are in the form of savings in long-term care for the traumatically injured who sustain permanent secondary damage. As mechanisms are better understood, new pharmaceuticals can be developed to target the specific causes of damage, reducing side effects and maximizing recovery.

It is vital to continue basic science research even after clinical discoveries have been made. As an example, a large, multi-centered clinical trial (National Acute Spinal Cord Injury II) showed that methylprednisolone (MP) improved neurological function after acute spinal cord injury if therapy were begun within eight hours. A second, small study showed promise of the ganglioside GM1 given within 36 hours of injury. The untested suggestion might be that the two drugs, given sequentially, would further improve function after a spinal cord injury. Fortunately, basic science work with a rat model of SCI allowed comparison of the two drugs, individually and in combination. Results have important ramifications for future clinical practice: individually, MP reduced lesion volume and GM1 showed no effect in the animal model, but the combination of the two drugs was detrimental in that the positive effect of methylprednisolone was blocked by the ganglioside. The concurrent use of the 2 drugs in human subjects is not indicated.

In this case, the preclinical testing of drugs for acute spinal cord injury has shown that certain drugs, alone or in combination, could be detrimental to efficacious treatment of acute spinal cord injury. Thus, the results not only guide therapy in important ways that can prevent further injury but also reduce health-care costs that would result from the use of contraindicated therapeutic agents.

Neurogenetics: A great number of opportunities exist to identify the genetic basis of a wide range of neurological disorders, and use that knowledge to improve diagnosis and develop therapeutic strategies. For instance, the genetic basis of epilepsy is an active area of research. Genes have been localized to chromosomes in three forms of the disorder; for example, the region of chromosome 21 linked to Baltic type progressive myoclonic epilepsy has a gene encoding part of a calcium binding protein. Research studies using the tools of molecular biology and transgenic animal studies, in which genes can be removed or over-expressed, offer opportunities to understand a range of neurological disorders, including stroke, and to understand the genetic basis for cognitive functions such as learning and memory.

Multiple Sclerosis: Multiple sclerosis (MS) is a chronic disease of the nervous system presumed to be of autoimmune origin. The myelin that surrounds nerve fibers in the brain and spinal cord is destroyed, fails to re-form, and develops into scar tissue resulting in neurological dysfunction. Progress in understanding and treating MS will come from research to characterize the genetic, viral, immune, and perhaps other unknown factors that have been implicated in the disease. The NINDS plans to continue to support fruitful avenues of research such as mechanisms of pathogenesis and plaque formation, role of heat shock proteins, remyelination, genetic susceptibility, clinical studies of cytokines, use of peptides in regulation/blocking of immune responses, development of new monoclonal antibodies, and studies of adhesion molecule function in cell traffic across the blood brain barrier.

Stroke: Stroke researchers are developing strategies to advance our knowledge of stroke through both new genetic and new immunologic technologies. The unprecedented rapid development of molecular genetics has revolutionized medical research, and these powerful genetic methods are now being used to study the pathogenesis of stroke. For example, transgenic technology provides a broad array of experimental approaches to test molecular, biochemical, and cellular hypotheses in intact animal models that over express superoxide dismutase and animals that do not express neuronal nitric oxide synthase in experimental stroke. Stroke investigators are also using molecular genetic approaches to identify familial clustering in some patients with intracranial aneurysms and subarachnoid hemorrhage that suggest a possible mode of inheritance.

RESEARCH PIPELINE

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Grady: The pipeline has been adequate but faces obstacles due to the increasingly non-competitive stipend levels provided by the NRSA program, although stipend levels were increased in FY 1994. This makes it difficult to attract the highest quality trainees, especially minorities and women, to NRSA programs since other sources of support are more generous. This is unfortunate since past evaluations of the NRSA program reveal that NRSA-trained individuals have better success rates than non-NRSA trained individuals. If we cannot attract the best neuroscientists to research careers, then research in areas of neurological science will suffer.

CLINICAL RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Grady: Despite its importance as the third most common cause of death and as an major cause of prolonged disability, until recently, treating stroke at the time it happens has not received adequate attention. Now, finally, a few things are beginning to happen. Some medical centers are beginning to treat stroke as a serious medical emergency, one that requires the same sense of urgency given to heart attack or trauma. This is especially good news for minorities and older Americans who are disproportionately affected by stroke. It is truly exciting to see doctors and nurses working together in the few stroke strike teams that have been established. The teams can actually cut through all the delay and get right to giving a drug treatment within just 30 to 40 minutes of the time they arrive in an emergency room. With cooperation from the emergency transportation services, the teams have been able to obtain this objective in hundreds of cases; they can actually begin treatment within 90 minutes of the time the stroke begins. For the first time, stroke patients are being treated at a time when findings from the laboratory tell us the drugs can actually work. This is exciting. Exciting both to finally see years of laboratory work coming to fruition and exciting to see medical teams working rapidly to give emergency treatment to the thousands of stroke victims that have been left waiting in the back of the emergency room for years. Expanding the number of these stroke treatment teams could be a critical factor in fostering better treatment for all.

Clearly, there would be tremendous benefit if thousands of individuals could spend several years or more without suffering the disability of stroke. In relation to financial benefits, there are those who could stay at home independently and self sufficiently rather than requiring expensive long-term care in a nursing home, which would have enormous consequences in health-care costs saved.

There are several other areas of clinical research opportunities. Studies of gene-based therapies for neurological disorders have been launched. NINDS will encourage new efforts in gene therapy for Duchenne's muscular dystrophy and has also joined with NIDDK to encourage new methods of gene therapy for inherited metabolic diseases such as Batten disease. Such approaches to therapy offer the chance to target the disease process, not just to treat symptoms, and to bring about long lasting improvement. We need to also improve understanding, diagnosis, and treatment of neurological disorders in infants and children, who can experience life-long, disabling consequences of neurological disorders and their adverse impact on educational and employment opportunities. NINDS recently established pilot research centers in neonatal brain injury which are part of NINDS efforts to stimulate new findings in this crucial area. Opportunities exist, also, to develop improved medications for epilepsy with fewer side effects, and to explore the use of surgery as a treatment for epilepsy.

The impact of trauma on the nervous system is tremendous. Trauma is the leading cause of death in Americans under 45 years of age, and brain injury is a major factor contributing to this death rate. Major emphases are placed on the prevention of secondary damage, regeneration and plasticity, and neurorehabilitation, including development of neural prostheses and methods to promote recovery of cognitive and language function following brain injury. NINDS held a workshop recently on traumatic brain injury in children which identified areas of research opportunities.

MINORITY HEALTH

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Grady: Minority populations are particularly impacted by many of the the diseases and disorders within the mission of the NINDS, including stroke, neuro-AIDS, diabetic neuropathy, head and spinal cord injury, developmental disorders, epilepsy, and neurological aspects of chemical use and dependency. NINDS seeks to understand and improve the health of minority citizens through a number of research initiatives. For example, NINDS is supporting a study at the University of Cincinnati that will provide the first comprehensive comparison of stroke incidence rates between African Americans and whites. A number of epidemiological surveys are being conducted to determine the frequency of seizure disorders and factors associated with the development of epilepsy in urban under-priviledged communities. NINDS is also supporting a study of the effect of neonatal cocaine intoxication and withdrawal in a San Francisco hospital. The population is largely African American, Hispanic, and Asian.

Also, the Division of Intramural Research supports a project encompassing a wide scope of statistical collaboration and consultation with laboratories and branches within DIR and other neuroscience units outside of the NIH. One of several ongoing projects involves studying the prevalence of neurological diseases in Navajo tribes.

NINDS provides support to components of the Minority Biomedical Research Support Program and the Minority Access to Research Careers Program that relate to research activities of the Institute. This intra-agency agreement is designed to help increase the representation of minorities in brain and nervous system research.

NINDS disseminates information to minority populations on the incidence, prevalence, prevention, and treatment of neurological disorders that have a significant impact on these population groups. The Institute prepares and distributes public information pamphlets on numerous diseases within its mission that fit this description, including stroke and epilepsy.

NINDS has published a program announcement to encourage research on "Strokes in Blacks, Other Minorities, and Women" and has a very active program in neuro-AIDS, a disease that impacts disproportionately on members of minority groups.

MINORITY SUPPLEMENTS

Mr. Stokes: I understand that a number of the institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Grady: The minority supplement program was initiated in April 1989, and NINDS has been an active participant since its inception. The program supports individuals from the level of high school student up to the level of faculty members. Faculty members and postdoctoral individuals who have received support through this program have not yet completed those projects and therefore have not had the opportunity to compete for independent support. The high school, undergraduate, and graduate students will not be able to submit applications for some years yet.

MINORITY RESEARCH

Mr. Stokes: How does your Institute identify its priorities for investments in minority research and research training?

Dr. Grady: NINDS is the focal point for research and research training to understand the brain and treat and prevent neurological and neuromuscular disorders that affect every age and segment of the population, including minority populations. For example, NINDS supports several research grants devoted in whole or in part to the study of peripheral neuropathy. Because of higher incidence rates among African Americans, Hispanics and Native Americans, the basic and clinical research supported will be of relatively greater benefit to these minority populations. NINDS continues to give priority to research that is focused on understanding the natural history and pathogenesis of diabetes, epilepsy, stroke, neuro-AIDS and low birthweight. The Institute continues to encourage and support studies that emphasize minority populations.

NINDS invests in the training of future research scientists. The Institute participates in an Adopt-A-School program that promotes the study of science among high school students and encourages them, especially minorities, to pursue research careers in the neurological sciences. Through the NINDS Summer Program in the Neurological Sciences, 60 minority students were awarded fellowships for research training positions in the Institute's Division of Intramural Research. NINDS will soon begin a pilot program to enhance research conducted on the campuses of minority institutions by facilitating further collaborations between neuroscience faculties and those of nearby institutions holding active research grants.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of historically black colleges and universities in biomedical research?

Dr. Grady: As part of our efforts to increase the participation of minorities in neurological research, NINDS supports traineeships for faculty members and students from HBCUs to participate in a course on biotechnology. In FY93, the NIH Office for Research on Minority Health provided matching support for 46 of these traineeships. The seven-day course provided insights and hands-on training and experience regarding the current thrust of biotechnology with special emphasis on recombinant DNA technology.

NINDS staff are developing a program to further career development of faculty at HBCUs as research scientists. NINDS also plans a workshop to bring together Institute staff, and minority faculty and postdoctoral individuals from HBCUs to advise and encourage individuals to apply for NINDS grant support. Program topics will include information on the grant application process, sources of funding available at various stages of a research career, as well as opportunities in the intramural program.

GS-15 EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Institute? How many employees in your Institute are in GS-15 and above positions? In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem in your Institute.

Dr. Grady: The NINDS, at this time, has 42 positions in grade 15 and above with 10 of them vacant. Among this group is one GS-15 African American who occupies the position of Deputy Executive Officer. The Institute has no African Americans among its pending requests for exceptions from the GS-15 and above freeze. There is one pending request for an exception from the promotion freeze to the grade 14 level for an African American. NIH has requested relief from the freeze but to our knowledge this has not been approved. If the freeze were lifted, it would enable NINDS to consider a much larger and more racially and ethnically diverse applicant pool when filling positions.

PREVENTION RESEARCH

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Grady: Until recently, prevention was not a common term in the neurological sciences. Neurological disorders were thought to be unpreventable because they were genetic, unpredictable (head and spinal cord injury), or poorly understood (stroke). Now we can report that we have the tools to prevent many disorders or, if they cannot be prevented in the first instance, we can prevent or reduce their impact. Today the NINDS research effort focuses on several major opportunities for disease prevention.

Advances in genetics offer the prospect of primary prevention through genetic counseling and gene therapy. Understanding the effects of genes and their products can also generate strategies for intervention such as replacement of missing enzymes, already shown to be beneficial in Gaucher's disease. We are also moving beyond the "one gene, one disease" model to explore the ways in which genetic predisposition may interact with environmental and other factors to cause disease.

Prevention of infant mortality and developmental disorders is a high priority for NINDS because of the vulnerability of the developing nervous system and the lifelong consequences of disorders of infancy and childhood. Through the recent establishment of centers for neonatal brain injury research and advances such as the use of indomethacin to treat and prevent intracranial hemorrhage in low birthweight infants, NINDS is investing in prevention research for our youngest citizens. Research directed at the prevention of epilepsy is of obvious benefit to children but also to people of all ages, since we are all potentially vulnerable to seizure disorders arising from head injury.

Stroke prevention remains a high priority in view of the high prevalence and enormous costs associated with stroke. Increasingly, large multi-centered clinical trials are being organized that are expected to answer long-standing questions of critical importance to stroke patients. NINDS supports clinical trials of medical and surgical approaches to prevent stroke as well as trials to evaluate new medicines to treat stroke soon after onset and improve recovery.

BIOTECHNOLOGY

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Grady: An estimated twenty-five percent of genetic disorders affect the nervous system; thus a great number of opportunities exist to identify the genetic basis of a wide range of neurological disorders, and use that knowledge to improve diagnosis and develop therapeutic strategies. For instance, the genetic basis of epilepsy is an active area of research. Research is also beginning to uncover the genetic basis for cognitive functions such as learning and memory. For example, an animal model has been developed in which a specific genetic defect in neurons has been linked to deficiency in a memory task. The development of transgenic animals, in which a particular gene can be over or under expressed, provides insights on that genes's normal function, and how abnormal activity might play a role in neurological dysfunction.

Further advances in understanding the molecular bases of neurological disorders opens the way to improved diagnoses, the development of gene-based therapies, and the development of new, targeted treatments. For example, new therapies may be designed to target a specific receptor or other component of a nerve cell; one advantage of such an approach would be the availability of more effective treatments with fewer side effects.

SUPPORT FOR MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Grady: The level of support that is estimated to be provided in Fiscal Year 1994 to minority institutions is $369,000.

Mr. Stokes: Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the institute's programs and activities?

Dr. Grady: NINDS is committed to improving the research capacity of minority institutions, especially the HBCUs. One important new initiative being planned is a faculty career development award for HBCU faculty. NINDS is also planning a technical assistance workshop for minority faculty--especially from HBCUs--to familiarize them with the grant application process and its nuances, as well as to have NINDS staff assist them in understanding program priorities and characteristics of successful grant applications.

MINORITY RESEARCH AND TRAINING

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training?

Dr. Grady: NINDS uses funds from various line items in its budget (research project grant, other research, NRSA) to support minority supplements, career development awards, and trainees. Recently, NINDS funded a grant from a minority investigator that had been assigned to another Institute and would otherwise not have been paid. We also funded a minority career development applicant who was beyond the original payline. NINDS staff will also maintain close contact with scientists who are funded through the minority supplement program to facilitate their subsequent success in applying for research grant support.

HIV DISEASE

Ms. Pelosi: As you know, recently more patients with advanced HIV disease are developing PML, an opportunistic infection of the brain which has apparently been significantly under-reported. Some doctors assert that PML is not treatable; others disagree. Can you tell us what studies you have undertaken on PML and what plans you have to answer the treatment options question?

Dr. Grady: NINDS support for neuro-AIDS research includes studies of the natural history of HIV-1 in the nervous system, the differing course and manifestation of neuro-AIDS in children and adults, the role of the immune system during viral infection and their effects on the brain, and the characterization of the onset and severity of neurological symptoms in HIV positive individuals. Progressive multifocal leucoencephalopathy (PML) is a neurological opportunistic infection that affects immunosuppressed AIDS patients. The condition, characterized by destruction of the myelin sheath of nerve cells, is caused by JC virus.

NINDS intramural investigataors have demonstrated that the drug cytosine arabinoside (ARA-C) can inhibit the replication and multiplication of the JC virus in cultures of human fetal glial cells at concentrations not toxic to normal cells. Additionally, they are collaborating with the NIAID-supported AIDS Clinical Trials Group (ACTG) providing laboratory support to evaluate tissue samples from AIDS patients being treated for PML. In early FY 1994, the NINDS awarded a new grant to a consortium of neurologists associated with the NIAID ACTG to focus on the neurological aspects of AIDS. Among the projects to be undertaken will be a controlled clinical trial of ARA-C in well documented and thoroughly followed PML patients, since ARA-C has only been used against PML in uncontrolled trials of individual patients with varying degrees of severity.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Ms. Pelosi: Does the NINDS intramural program have any beds or facilities in the NIH's clinical center devoted to studying patients with ALS?

Dr. Grady: NINDS has beds to study ALS patients. During the last year approximately 15 patients with ALS have been admitted.

Ms. Pelosi: How much space in clinical centers is dedicated specifically to studies involving ALS patients?

Dr. Grady: In addition to clinical beds, DIR, NINDS, uses 3,750 square feet of space for ALS basic and clinical research.

Ms. Pelosi: What is the intramural program at NIH doing to follow up on the SOD discovery?

Dr. Grady: NINDS is initiating a new pilot protocol using a drug with strong oxygen radical scavenging capabilities to treat some familial ALS patients with SOD deficiency. Two sisters with familial ALS, studied over the last 3 months, will receive this drug.

Ms. Pelosi: How many staff members in the intramural program at NINDS are spending their entire effort or the major portion of their efforts on ALS research?

Dr. Grady: The total basic and clinical ALS research effort represents 16.4 full-time equivalent positions.

GUAMANIAN ALS

Ms. Pelosi: Observe that much of the research effort on ALS within NINDS has been on patients with Guamanian ALS (occuring in Guam). What scientific results have come from these studies that have been of help to patients with ALS in the Continental U.S.?

Dr. Grady: Amyotrophic lateral sclerosis (ALS), known locally on Guam as lytico or paralytico, is clinically indistinguishable from sporadic (non-familial) ALS in the continental United States and worldwide. The onset of symptoms in invariably insidious and progressive, leading uniformly to death in several years. After the identification of a 50-fold higher incidence of ALS on Guam compared to the continental United States, the NINDS (then known as the NINDB), established a research center on the island in 1956 in an attempt to understand the causal factors involved, and the mechanisms by which it progresses with an ultimate aim toward treatment and prevention. The Research Center on Guam was effectively closed 27 years later in 1983.

During the past few decades, scientists representing many disciplines have studied foci of ALS not only on Guam, but in two other high-incidence foci in West New Guinea and the Kii Peninsula of Japan, each occurring in different cultures, in different ecological zones and among genetically divergent populations. This work has enhanced our understanding of ALS and other neurodegenerative disorders, including parkinsonism, Alzheimer's disease, and early neuronal aging.

Biomedical scientists have recognized the importance of studying intense foci of disease over limited geographic areas. These foci of disease occur in populations that are small, culturally or geographically isolated, and genetically homogeneous, providing a natural laboratory and insights that would not be forthcoming from studies in large cosmopolitan western communities, where confounding factors often complicate conventional research strategies.

Specifically, we know from studies of ALS on Guam and among the other two Pacific foci that for the past four decades ALS has dramatically declined to levels approaching what we see in the continental United States. This decline strongly suggests that environmental factors play a major role in the disease process. We also know that systematic studies on Guam have provided no evidence for a genetic cause nor the identification of an infectious agent, although epidemiological and cellular and molecular studies have provided significant thinking about toxic causes. The world neurological community has and continues to look to Guam and the other foci as natural models to clarify our understanding about ALS.

Likewise, as new research and theories are generated from ALS patients in the continental United States and elsewhere, the world scientific community expects that these theories, questions and research approaches will be investigated on Guam.

Simply stated, the systematic study of ALS on Guam has provided much of what we know about ALS worldwide. The importance of Guamanian ALS to ALS occurring elsewhere is emphasized in every major textbook of neurology. Clinicians and neuroscientists all over the world are familiar with how studies of ALS on Guam and the other Pacific foci have contributed to our understanding about ALS in the continental United States and worldwide. None of these scientific advances could have been possible without the extraordinary cooperation of the Chamorro people of Guam to whom the medical community owes a great debt.

ALS PATIENTS

Ms. Pelosi: How many ALS patients are involved in clinical investigations conducted by the intramural program of NINDS?

Dr. Grady: NINDS, DIR, has completed a trial using high-dose intravenous immunoglobulin (IVIg) in 10 ALS patients. This was a 5 month study in which ALS patients were treated with monthly infusions of IVIg. The rationale for this study was based on the possibility that ALS has an autoimmune component and that the serum IgG is an antibody directed against a calcium channel. The infused immunoblobulin contains a variety of autoantibodies that could, theoretically, compete with the patient's putative pathogenic IgG. The intramural NINDS investigators who conducted the study found that IVIg was of no benefit to ALS patients.

Four additional patients have been involved in a pilot study of special MRI studies.

ALS: INTRAMURAL AND EXTRAMURAL

Ms. Pelosi: How does the research done on ALS in the intramural program of NINDS cooperatively relate to work done on ALS in non-federal research institutions?

Dr. Grady: Tissues from patients with familial ALS have been sent to extramural investigators involved with this work.

Ms. Pelosi: What are the total funding amounts in FY93 and FY94 for ALS intramural research and ALS extramural research?

Dr. Grady: The following table displays funding for ALS in Fiscal Years 1993 and 1994.

Amyotrophic Lateral Sclerosis (ALS)
(Dollars in thousands)

	FY 1993 Actual	FY 1994 Estimate
Extramural	$5,367	$5,619
Intramural	2,884	2,855
Total	8,251	8,474

Ms. Pelosi: What new research grants have been awarded for ALS research since FY93?

Dr. Grady: To date in FY 1994 new ALS research grants have been awarded in the following areas: Identification and transgenic studies of ALS genes, model of human motor neuron disease, trophic factors in chronic motor neuron degeneration, and cyclic AMP and neuronal programmed cell death.

Ms. Pelosi: How is NINDS manifesting Congressional will that ALS is a "high priority?"

Dr. Grady: ALS research has been and continues to be a high priority for NINDS. It is a devastating, fatal disorder, and while it is not common, the prevalence of about 14,000 in the United States is higher than many of the rare neurological disorders.

Last year's discovery of a gene for ALS opened up research opportunities that hold promise not only for those afflicted with ALS, but for several other disorders. Equally exciting is the discovery that the gene codes for production of an enzyme, superoxide dismutase, that is thought to play a key role in many neurodegenerative disorders.

PREVENTION

Ms. Lowey: In the area of prevention, your testimony mentions that the Institute plans to publish two brochures addressing patient education and stroke prevention. Can you tell us more about the nature and goals of this project?

Dr. Grady: NINDS plans for this year a publication on the prevention of stroke and we have received clearance to do a revision of a public information pamphlet on stroke, "Hope through Research" in Spanish and in English.

In addition, NINDS staff have prepared a bookmark on risk factors for and warning signs of a stroke, to be handed out at health fairs and other events where the general public can be easily reached, and an update of NINDS Stroke Research Highlights pamphlet. The pamphlet is a low-cost, straightforward summary of new research findings, initiatives, and goals concerning stroke.

STROKE

Ms. Lowey: What can you tell the Committee about the progress of studies to determine whether estrogen can decrease the risk of stroke in postmenopausal women?

Dr. Grady: Previous epidemiologic studies suggest that postmenopausal estrogen therapy may reduce the risk of death from cerebrovascular disease in postmenopausal women. To address questions surrounding the use and benefits of such therapy, in 1993, NINDS initiated a clinical trial to determine whether estrogen therapy reduces the risk of death or recurrent stroke in postmenopausal women who have had a recent transient ischemic attack or non-disabling stroke (both conditions which place these women at greater risk for recurrent stroke). Over 15 centers and hospitals are participating in this study. Patients will be followed for a period of up to 4.5 years.

PARKINSON'S DISEASE

Ms. Lowey: Can you update the Committee on the Institute's progress in working with other Institutes toward developing a coordinated research agenda on Parkinson's Disease.

Dr. Grady: In response to a request from the Senate Appropriations Committee for a report on this topic, NINDS surveyed the NIH ICDs to identify research activities related to Parkinson's disease. The report documents a robust and varied program of research directed or relating to Parkinson's disease, totalling $71.9 million for NIH in FY 1993. Major participants include NINDS, as the lead institute for this major neurological disorder; the National Institute on Aging, with special interest in Parkinson's as a disorder with higher incidence in the aging population; the National Institute of Mental Health, focusing on neurobiological and behavioral aspects; and the National Institute of Environmental Health Sciences, which supports research investigating possible environmental influences on Parkinson's disease. Other ICDs have a research intrest in the biology of the brain as it is relevant to Parkinson's disease--for example, the study of neurotransmitters, receptors, and tissue implants.

The report concluded that longstanding NIH research management practices are adequate to ensure coordination of Parkinson's disease research. These include the guidelines for assignment of incoming applications to the appropriate review group and funding unit; requirements that all program solicitations be circulated for review, comment, and possible cosponsorship prior to publication; committees and task forces in areas of common interest, such as aging research; and opportunities for intramural collaborations.

ALZHEIMER'S DISEASE

Ms. Lowey: What is the nature of the Institute's contribution to research on Alzheimer's Disease?

Dr. Grady: NINDS supports and conducts research in Alzheimer's disease (AD) focused on discovery and increased understanding of the cellular and molecular defects and underlying mechanisms involved in the disease. Exciting discoveries in Alzheimer's disease (AD) research have occurred across a broad range of endeavors. For example, the gene specifying the beta-A4 amyloid protein of the normal aging brain and Alzheimer's disease was first isolated, sequenced, characterized, and chromosomally localized by NINDS scientists in 1985. Most recently, intramural research on potassium channels--small openings that regulate the movement of ions in and out of cells--pointed to potassium channel dysfunction in patients with Alzheimer's disease. Examination of skin cells from Alzheimer's patients have revealed defects in the regulation of potassium ions. These same investigators found that the addition of beta-amyloid to normal skin cells prevents potassium channels from functioning, thus changing normal cells to resemble Alzheimer's cells.

Promising areas for continued research progress intramurally and extramurally include the molecular genetics of AD, the role of neurotrophic factors, the biochemical and immunochemical analysis of the neuropathological characteristics which define AD, and brain imaging studies to understand how the brain is changing in the earliest stages of the disease and then relate these findings to genetic, metabolic, and cellular studies.

HISPANIC HIRING

Mr. Serrano: First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Grady: We are recruiting and training Hispanics for the Institute's postdoctoral research training programs and tenured research investigator positions. These activities provide academically talented students a unique opportunity to acquire valuable hands-on research training and experience in the neurological sciences. NINDS encourages students to pursue careers in biomedical research and academic medicine, especially basic and clinical neurosciences. Eleven Hispanic students have been selected for positions in the 1994 NINDS Summer Program in the Neurological Sciences.

We have implemented outreach initiatives in the Institute to help stimulate interest in research training opportunities in brain and nervous system research supported by the NINDS. For example:

The Institute conducts outreach and sponsors workshops and laboratory tours for Hispanic high school students participating in the National Hispanic Youth Initiative in Health and Policy Development (105 students in FY 1993). Please note: several students that were participants in the program have been selected for positions in the NINDS Summer Program in the Neurological Sciences.

Staff members from the Institute attended the 1994 Society for Advancement of Chicanos and Native Americans in Science Annual Conference that was held in Chicago and they recruit at the conference every year. Institute representatives held meetings with students, faculty members, program directors, and predoctoral and postdoctoral trainees to present and discuss career and research training opportunities in the neurological sciences supported by the NINDS. Four science students that were participants at the meeting have been selected for positions in the Institute's Summer Program in the Neurological Sciences.

To help attract and train a cadre of Hispanic scientists for the next century, the Institute will be providing funds (approximately $377,000) in FY 1994 to support Hispanics students and scientists who are training for careers in the neurological sciences. The awards are made as supplements to NINDS research grants to support components of the NIH initiatives for underrepresented minorities in biomedical research.

HISPANIC HEALTH

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Grady: A significant proportion of the NINDS research program is directed at health problems of special concern to

Hispanics. Most neurologic disorders, broadly viewed, show no racial or ethnic preference. Increasingly, however, there is interest in exploring how specific populations may vary in risk factors. Thus stroke is a major health problem for all groups, but we are learning through epidemiological studies that Hispanic people face a higher risk because diabetes--which is higher in Hispanics than in the general population--is a major risk factor for stroke. Similarly, Hispanics are at risk for the neuropathy that often accompanies diabetes. On an even more focused level, since many neurological disorders have a genetic basis, research into disorders more common in Hispanic populations offers additional challenges and opportunities to improve the health of Hispanics.

NINDS also places high priority on research affecting the health of infants, children, and young adults. These efforts are of special interest to Hispanics because of the increases in the Hispanic population and the importance of economic wellbeing and access to care as it may affect infant mortality, developmental disorders, including epilepsy, and head and spinal cord injury.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Grady: NINDS is working to increase participation of Hispanics in neurological science research through the Research Supplements for Underrepresented Minorities (RSUM) program (implemented in 1989), support of the annual meeting of the Society for the Advancement of Chicanos and Native Americans in Science (SACNAS), and annual support of the Minority Biomedical Research Support program. In the past year and a half, NINDS has supported 22 Hispanic individuals through the RSUM program, including 4 undergraduates. The RSUM program includes a high school student component, but NINDS has not yet had any Hispanic applicants for this support.

HISPANIC PARTICIPATION IN CLINICAL TRIALS

Mr. Serrano: Fourth, what is your institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Grady: NINDS is aggressively implementing the NIH guidelines for inclusion of women and minorities in clinical research. Applicants for clinical trials must address not only the intended inclusion of Hispanics in their study populations but also their plans for outreach to potential Hispanic participants. Such plans must include strategies for both recruitment and retention of participants. The institute will distribute to all current clinical trial investigators, as well as to prospective applicants, the guide for outreach efforts that is currently being developed by the NIH Office of Research on Minority Health and the Office of Research on Women's Health. In an effort to increase Hispanic participation in an ongoing trial of gene therapy for brain tumors, the Institute sought assistance from the Hispanic Medical Society.

HISPANIC INVESTIGATORS

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Grady: In FY 1993 NINDS received 35 research project grant applications from investigators who identified themselves as Hispanics. This represented 2 percent of the total applications. Awards were made to 8 of the Hispanic investigators, which is also 2 percent of the total awards. The success rate for Hispanic applicants was 22.9 percent, which does not differ significantly from the overall NINDS success rate of 24.7 percent.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

HIGH RISK RESEARCH PROJECTS

Mr. Smith. Describe for us your new system of setting aside a certain amount of funding to ensure support for higher risk research projects. How does your effort differ from the Shannon awards?

Dr. Cassman. In recent years, the National Advisory General Medical Sciences Council has become concerned that the research portfolio of the NIGMS is no longer as diverse as could be wished. The Council felt that this might be due to an increasing conservatism in the review of proposals and the selection of research programs to be funded, both of which tend to favor proposals for which the productivity of the research is virtually assured. It results in funding being concentrated in areas that are currently highly productive and intensely active. Such research is immensely valuable and must be encouraged in order to take full advantage of the opportunities provided by breakthrough discoveries. At the same time, the Institute must provide incentives to explore relatively unknown and risky areas, and to increase the diversity of its portfolio in areas that might potentially result in future breakthroughs. Thus, the Institute has set aside up to 5% of its competing research project grant funds for its Scientific Diversity Awards. The awards provide a modest level of support for high risk applications which may have high payoff, but which are outside the normal funding order.

The Shannon program is intended to:

1. encourage the exploration of new and exciting ideas that might become fundable if they had the benefit of a small amount of support for the purpose of generating a limited amount of data;

2. support novel proposals that whose success is uncertain, but have a high potential payoff if proven successful; or

3. support bright, young investigators trying to establish a research career.

The Scientific Diversity Awards and the Shannon Program have in common only element number 2 (above). However, the motivation for the NIGMS Scientific Diversity Awards includes the purpose of increasing the diversity of the Institute's research portfolio.

SUCCESS RATES

Mr. Smith. Explain the reasons behind the dramatic increases in the 1995 success rates for your research grants.

Dr. Cassman. The success rate for FY 1995 will be 38 percent. The reason for this is that over one-third of our research grant portfolio will turn over in FY 1995.

Mr. Smith. Why is this higher than most other NIH Institutes?

Dr. Cassman. The high turnover rate is the consequence of our funding behavior in FY 1991 and FY 1992. In FY 1991, most of our new and competing grants were awarded for five years. In FY 1992, Congress mandated, as part of the NIH cost management plan, that our research projects be limited to an average length of four years. As a result of those two past years' worth of grants coming to an end, the turnover this year in our noncompeting pool is much larger than normal, and is underwriting a large increase in the number of competing applications that can be funded.

Mr. Smith. You are predicting more than a 50 percent increase in the number of new grants in 1995. What impact does this have on the stability of your research portfolio and your long-range planning efforts?

Dr. Cassman. Although there will be a 50 percent increase in the number of new and competing research projects in 1995, this translates into an increase in NIGMS's total grants funded of only 54 more than in FY 1994. Certainly, the cyclical nature of competing grant application pressures creates significant uncertainties in the research community served by NIGMS about the probability of competing successfully for funding.

Mr. Smith. Without substantial increases in funding, will you have years with very low success rates in the future?

Dr. Cassman. Based on the cyclical nature of grant terminations and on grant application pressures, the NIGMS success rate may exhibit some fluctuations.

NRSA STIPENDS

Mr. Smith. Tell us more about the decision to increase the 1994 training stipend for first-year pre- and postdoctoral trainees and the impact it has had on the number of traineeships awarded.

Dr. Cassman. The NIH received approximately $23 million in increased allocations for NRSA research training in fiscal year 1994. Since stipends had not been increased since fiscal year 1991, NIH elected to use about half of the new allocations to increase graduate stipends by $1,208 and the first two years of postdoctoral stipends by $1,000. The $23 million increase would have supported approximately 1,000 new training positions in fiscal year 1994 prior to the stipend increase. With the stipend increase, the NIH was still able to increase training positions by approximately 300. Of that number, the increase for NIGMS was 182 training slots.

Mr. Smith. Does your budget assume further increases in stipends in 1995?

Dr. Cassman. The FY 1995 budget does not assume another stipend increase.

RESEARCH TRAINING

Mr. Smith. What percentage of all research training is supported by NIH funding?

Dr. Cassman. The Survey of Graduate Students and Postdoctoral Training conducted by the National Science Foundation and the Survey of Earned Doctorates conducted by the National Academy of Sciences indicate that NIH National Research Service Awards (NRSA) support between 11 and 15 percent of all graduate students in biomedical sciences. In behavioral sciences, NRSA programs support approximately four percent of all graduate students. Estimates of the pool size for postdoctoral scientists are not considered reliable, so it is not clear what part of the total pool is represented by the nearly 7,000 postdoctoral trainees and fellows supported by the NIH.

NAS REPORT ON RESEARCH TRAINING

Mr. Smith. What can you tell us about the forthcoming National Academy of Sciences report on future research training needs?

Dr. Cassman. The executive summary of the tenth NAS report on National Needs for Biomedical and Behavioral Research was released on April 19. The Committee on Research Personnel Needs remains very supportive of the National Research Service Awards (NRSA) and states that

> "...although the NRSA program may be relatively small as regards total numbers of trainees (less than 15 percent of the total number of graduate students training in the biomedical and behavioral sciences are supported by NRSA funds in any year), it is enormously powerful in its ability to change research emphases and to attract the highest quality individuals to research careers."

The Committee makes the following recommendations:

- Raise the real value of stipends to more competitive levels: approximately $12,000 per year for predoctoral awardees and approximately $25,000 for postdoctoral awardees with less than two years of research experience. Maintain the real value of these stipends through annual increases of three percent per year.

- Maintain the annual number of predoctoral awards in the basic biomedical sciences at 1993 levels, or approximately 5,175 awards, and the number of postdoctoral awards at 3,835.

- Increase the annual number of NRSA awards for research training in the behavioral sciences from 1,069 to 1,450 between 1993 and 1996.

- Increase the number of Medical Scientist Training Program (MSTP) awards each year from 822 in 1993 to 1,020 by 1996 and the number of postdoctoral fellows in the clinical sciences from 68 in 1993 to 160 in 1996. To achieve this expansion, we recommend that the annual number of postdoctoral trainees in the clinical sciences be decreased slightly from 2,051 to 1,805 between 1993 and 1996.

- Increase the number of awards in oral health research to 430 by 1996, in nursing research to 500 by 1996, and in health services research to 360 by 1996.

- Hold Minority Access to research Careers (MARC) awards constant at fiscal 1993 levels, or approximately 680 trainees, pending the outcome of the present NIH evaluation study.

- Examine research training opportunities for women throughout the NRSA program and strengthen the role of postdoctoral support to assist women in establishing themselves in productive careers as research scientists.

- Review NIH databases as management information systems and introduce changes in data collection, analysis, and dissemination to permit more effective tracking of NRSA award recipients. Emphasis should be given to the analysis of minority participation in research and training. New funds should be directed to the evaluation of NRSA program outcomes.

In this report, the NAS eschewed reliance on strict mathematical models and moved to an analysis of short-term indicators of labor market balance coupled with the use of multi-state life tables to model the supply of human resources. The Committee used expert opinion to estimate changes in future labor market demand. This approach seems to have more face validity than previous approaches. A thorough analysis of the methodology will be available in a report to be issued in August 1994.

ELIGIBILITY FOR MINORITY PROGRAMS

Mr. Smith. Your program of special initiatives for minorities focusses eligibility on minority students, rather than the institutions they attend. Is this shift in emphasis also appropriate for your longstanding minority programs such as MARC?

Dr. Cassman. We have a variety of programs that were developed to increase the number of minorities in the doctoral level biomedical research labor force. Our older programs including MARC and MBRS were developed to support research training for undergraduates and to enhance the capacity to conduct research at colleges and universities with substantial minority enrollments. These schools continue to be a focus of our efforts to recruit minority students. We are also concerned about the other 60 percent of minority undergraduates that attend majority schools. To reach these individuals we have recently developed a series of awards including research supplements for underrepresented minorities and national minority graduate fellowships. Our hope is that we can identify qualified minorities in all relevant settings and provide the support and training they need to become productive independent investigators.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Smith. How many historically black colleges and universities receive traditional NIH research training grants as opposed to MARC grants?

Dr. Cassman. There are currently five traditional NIH research training grants awarded to Historically Black Colleges and Universities. Four of these are awarded to Meharry Medical College in Nashville, Tennessee, and the fifth is awarded to Jackson State University, in Jackson, Mississippi.

MINORITY ACCESS TO RESEARCH CAREERS PROGRAM

Mr. Smith. Provide a 1993-1995 mechanism table for the MARC program.

Dr. Cassman. Below is the FY 1993-FY 1995 mechanism table for the MARC program.

Minority Access to Research Careers Program
(dollars in thousands)

	FY 1993		FY 1994		FY 1995	
	No.	Amount	No.	Amount	No.	Amount
Training:						
Individual	79	$1,779	96	$2,373	101	$2,492
Institutional	559	11,324	599	12,593	630	13,222
Total	638	13,103	695	14,966	731	15,714

Mr. Smith. How many trainees are supported by the MARC program 1993-1995?

Dr. Cassman. In FY 1993, NIGMS supported 638 MARC trainees. NIGMS estimates that it will support 695 trainees in FY 1994 and 731 trainees in FY 1995.

MINORITY BIOMEDICAL RESEARCH SUPPORT PROGRAM

Mr. Smith. Identify the 1993-1995 funding provided for the MBRS program from NIGMS and all other NIH institutes.

Dr. Cassman. The table below displays FY 1993-FY 1995 funding for the MBRS program.

Minority Biomedical Support Program
(dollars in thousands)

	FY 1993		FY 1994		FY 1995	
	No.	Amount	No.	Amount	No.	Amount
NIGMS........	98	$32,795	98	$34,795	103	$36,535
NCI..........	--	2,959	--	3,099	--	3,223
NHLBI........	--	2,540	--	2,647	--	2,753
NIDR.........	--	77	--	186	--	196
NIDDK........	--	1,659	--	1,745	--	1,794
NINDS........	--	290	--	221	--	235
NIAID........	--	1,010	--	1,052	--	1,105
NICHD........	--	513	--	569	--	585
NEI..........	--	287	--	338	--	364
NIEHS........	--	460	--	462	--	480
NIA..........	--	928	--	882	--	907
NIAMS........	--	420	--	430	--	452
NIDCD........	--	320	--	530	--	575
NCRR.........	--	0	--	0	--	0
NIMH.........	--	0	--	0	--	0
NIDA.........	--	0	--	0	--	0
NIAAA........	--	206	--	300	--	312
Subtotal.....	98	44,464	98	47,256	103	49,516
NIH - Office of Minority Health.......	--	602	--	--	--	--
TOTAL MBRS...	98	45,066	98	47,256	103	49,516

Mr. Smith. Identify how much MBRS funding is allocated to the traditional program versus the undergraduate college program.

Dr. Cassman. In FY 1993, $42 million or approximately 93 percent of MBRS funding was allocated to the traditional program. The remaining seven percent, or $3 million, was allocated to the undergraduate college program.

NRSA STIPENDS

Mr. Smith. Provide the range of pre- and postdoctoral research training stipends for 1994.

Dr. Cassman. In FY 1994, predoctoral trainee stipends were increased from $8,800 to $10,008 and postdoctoral trainee stipends will range from $19,600 to $37,100 rather than the previous $18,600 to $37,100.

MSTP AND BIOTECHNOLOGY TRAINING

Mr. Smith. Identify the number of trainees in your M.D.-Ph.D. program and your biotechnology program 1993-1995, compared to the initial goals set for these programs.

Dr. Cassman. In FY 1993, NIGMS supported 822 Medical Scientist Training Program (MSTP) trainees. NIGMS estimates that it will support 836 MSTP trainees in FY 1994 and FY 1995 which will bring NIGMS closer to reaching our initial goal of 1,000 trainees.

In FY 1993, NIGMS supported 353 biotechnology trainees. NIGMS estimates that it will support approximately the same number in both FY 1994 and FY 1995. NIGMS's initial goal was to support 1,500 biotechnology trainees by FY 1993.

IMPACT OF BASIC CANCER-RELATED RESEARCH

Mr. Stokes. According to the Congressional justification, the Institute is supporting research in cancer clues from drug metabolism variation. Can you tell us what has been some of the outgrowth of that investment?

Dr. Cassman. NIGMS supports several researchers working on identifying the basic differences in drug metabolizing enzymes. This work is particularly concentrated on the cytochrome P450 enzymes, because that family is known for biotransforming many substances, both natural (for example, substances found in plants) and nonnatural (for example, manmade chemicals). It is now well known that all individuals have unique profiles of cytochrome P450 enzymes based upon their heredity (including their ethnic background and sex) and their daily lifestyle (including their diet and environmental exposure). By knowing an individual's particular complement of cytochrome P450 enzymes, it may be possible to "read the clues" and predict whether or not that person may be inclined to develop certain cancers. The relevant work supported by NIGMS deals with developing safe, noninvasive tests to identify an individual's profile of cytochrome P450 enzymes. Generally, that is accomplished by administering a safe, nontoxic, well-understood "probe" compound. The researcher then monitors the individual over time, performing a variety of tests to detect how the "probe" compound has been changed or biotransformed into a new structure. Based upon the biotransformation of the "probe" drug structure, it can be inferred which cytochrome P450s were present in that person, thus the person can be "typed." One of the future outgrowths of this research will be easy-to-do typing of all patients so that a physician can recognize the clues and predict how that individual's unique enzymatic make-up will predispose him or her to developing particular diseases.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes. The demographics of our younger generation are changing, with minority young people representing a greater proportion of the student bodies of the colleges and universities across the country. Given this trend, how much of the NIGMS support for MBRS, MARC, and Bridges Programs is going to the schools, such as HBCUs, for which the programs were originally intended when they were established over 20 years ago?

Dr. Cassman. Of the 104 institutions with active MBRS grants, 51 are HBCUs. NIGMS provides $13.7 million to these institutions with other components of NIH providing another $5.5 million in cofunding. Of the 69 institutions with MARC grants, 36 are HBCUs. NIGMS provides $5.9 million to these institutions, with other components of NIH providing $400 thousand. In addition, a significant number of faculty fellowships and predoctoral fellowships go to individuals pursuing their studies at HBCUs. With regard to the Bridges Programs, five HBCUs are participating and receive $1.4 million.

Mr. Stokes. What are you doing to ensure that such institutions can continue to play a major role in preparing the next generation of biomedical scientists?

Dr. Cassman. Through ongoing discussions with representatives from these institutions, as well as through the regional workshops the Institute has held over the past three years, NIGMS continues to encourage the participation of HBCUs and other, similarly focused institutions, in the MBRS and MARC programs, as well as in the Bridges Program. In addition, the Institute has limited the percentage of the funds for the MBRS program that may be given to the component of the program in which more research-intensive institutions may participate. In effect, this reserves 85 percent of the MBRS funds for institutions such as HBCUs.

Mr. Stokes. Provide for the record, a chart displaying the funding history for each of these programs (MBRS, MARC, and Bridges) since their inception and the percent change between years. Also show the total appropriation amount received by the Institute for each of the respective years and their percent change?

Dr. Cassman. Below is a table displaying the funding history for the MARC Program, the MBRS Program, and the Bridges Program. Also included is the funding history for the Institute's total budget.

History Table
MARC, MBRS, and Bridges Programs 1/
(dollars in thousands)

	FY 1971	FY 1972	FY 1973	FY 1974	FY 1975
MARC		$151	$241	$4,465	$423
(% change)		(N/A)	(59.6%)	(1,752.7%)	(-90.5%)
MBRS 2/		$2,000	$6,000	$7,000	$7,270
(% change)		(N/A)	(200.0%)	(16.7%)	(3.9%)
Bridges					
(% change)					
Total NIGMS	$159,841	$173,337	$154,036	$188,605	$187,229
(% change)	(N/A)	(8.4%)	(-11.1%)	(22.4%)	(15.5%)

	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980
MARC	$350	$1,788	$2,571	$2,870	$4,310
(% change)	(-17.3%)	(410.9%)	(43.8%)	(11.6%)	(50.2%)
MBRS 2/	$7,610	$9,711	$10,758	$14,609	$18,089
(% change)	(4.7%)	(27.6%)	(10.8%)	(35.8%)	(23.8%)
Bridges					
(% change)					
Total NIGMS	$220,706	$204,758	$230,415	$277,259	$312,415
(% change)	(17.9%)	(-7.2%)	(12.5%)	(20.3%)	(12.7%)

Note: 1/ These figures exclude funding from other ICDs.
2/ MBRS program primarily funded by the Division of Research Resources from FY 1972 to FY 1990. MBRS program primarily funded by the National Institute of General Medical Sciences from FY 1991 to the present.

History Table
MARC, MBRS, and Bridges Programs 1/
(dollars in thousands)

	FY 1981	FY 1982	FY 1983	FY 1984	FY 1985
MARC	$4,515	$5,413	$5,975	$6,012	$7,741
(% change)	(4.8%)	(19.9%)	(10.4%)	(0.6%)	(28.8%)
MBRS 2/	$18,852	$18,065	$19,747	$21,879	$24,951
(% change)	(4.2%)	(-4.2%)	(9.3%)	(10.8%)	(14.0%)
Bridges					
(% change)					
Total NIGMS	$333,504	$339,837	$369,810	$415,896	$480,975
(% change)	(6.3%)	(1.9%)	(8.8%)	(12.5%)	(15.6%)

	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990
MARC	$7,950	$8,566	$8,709	$9,053	$10,670
(% change)	(2.7%)	(7.7%)	(1.7%)	(3.9%)	(17.9%)
MBRS 2/	$23,878	$28,178	$28,342	$28,147	$29,794
(% change)	(-4.3%)	(18.0%)	(0.6%)	(-0.7%)	(1.0%)
Bridges					
(% change)					
Total NIGMS	$493,535	$570,867	$632,624	$682,134	$680,305
(% change)	(2.6%)	(15.7%)	(10.8%)	(7.8%)	(-2.7%)

	FY 1991	FY 1992	FY 1993	FY 1994	FY 1995
MARC	$13,220	$13,514	$13,103	$14,966	$15,714
(% change)	(23.9%)	(2.2%)	(-3.0%)	(14.2%)	(5.0%)
MBRS 2/	$31,614	$33,190	$32,795	$34,795	$36,535
(% change)	(6.1%)	(5.0%)	(-1.2%)	(6.1%)	(5.0%)
Bridges 3/		$2,600	$9,047	$12,000	$12,000
(% change)		(N/A)	(248.0%)	(32.5%)	(0.0%)
Total NIGMS	$761,231	$818,297	$832,235	$875,511	$907,598
(% change)	(11.9%)	(7.5%)	(1.7%)	(5.2%)	(3.7%)

Notes: 1/ These figures exclude funding from other ICDs.
2/ MBRS program primarily funded by the Division of Research Resources from FY 1972 to FY 1990. MBRS program primarily funded by the National Institute of General Medical Sciences (NIGMS) from FY 1991 to the present.
3/ The Bridges Program is funded by the NIH Office of Minority Health and administered by NIGMS.

NEW INITIATIVES FOR MINORITY STUDENTS

Mr. Stokes. Have you established any new initiatives to reach minority students who attend majority colleges and universities?

Dr. Cassman. In recent years, NIGMS established several new initiatives that are intended to reach minority students who attend majority colleges and universities. The National Predoctoral Fellowship Program, initiated in Fiscal Year 1991, provides predoctoral fellowship support to minority students enrolled in graduate schools throughout the country. The Bridges Program, initiated in Fiscal Year 1992, is designed to address two problems. First, it was designed to help minority students "bridge" the gap between two-year junior or community colleges and four-year universities, in recognition of the fact that many minority students begin college in community colleges and might be "lost" to science careers at the end of their second year of college. Second, the Program established a bridge between universities granting the Master's degree in Science as the terminal degree and universities granting a doctoral degree. While NIGMS manages the two Bridges Programs, the funding is provided by the NIH Office of Research on Minority Health. Other programs which enable minority students to attend majority colleges and universities include the traditional research training grant programs, and the program of Research Supplements to Underrepresented Minorities. This latter program allows minority college students, graduate students, and postdoctoral students, among others, to be supported in the budget of a research grant, to enable them to receive training in biomedical research.

MINORITIES SUPPORTED ON NRSA TRAINING GRANTS

Mr. Stokes. NIGMS is still the leader at NIH in support for research training programs generally. What is the Institute doing to increase the number of underrepresented minorities who participate in and benefit from its regular research grant training programs?

Dr. Cassman. Since 1989 all NIH institutional research training grant applicants have been required to describe their plans for recruiting and retaining underrepresented minorities in their training programs. The plans are evaluated by the members of the initial review group who rate them as "acceptable" or "unacceptable" Only those that are rated "acceptable" are considered for funding. Applicants whose plans are not satisfactory are notified and required to submit an acceptable plan.

In July 1993 the NIH announced that the adequacy of the recruitment and retention efforts and the success in identifying and appointing minority trainees during the previous training grant award period would also be factors considered by the initial review group when those grants are submitted to recompete for support. This evidence is also considered by Institute staff when funding decisions are made.

NIGMS staff and a working group of the National Advisory General Medical Sciences Council have developed guidelines for handling programs with problems in recruiting underrepresented minorities. They have also developed a document which describes approaches and techniques used by some of the institutions that have been successful in recruiting underrepresented minorities into their programs. This document is shared with all applicants and training grant program directors in hopes that successful strategies can be emulated.

IMPACT OF BASIC RESEARCH

Mr. Stokes. African-Americans and other ethnic minorities frequently have an increased incidence of many serious health disorders, including cancer, stroke, and hear disease. What role does the basic research supported by NIGMS play in addressing this problem?

Dr. Cassman. The NIGMS supports research in a broad range of fundamental disciplines. Findings from this basic research have been shown to have an impact on many diseases. For example, recent reports have demonstrated that the discoveries of NIGMS investigators in areas such as cell division and repair of DNA, lead to the ability to identify and understand the genetic defects in inherited forms of cancer. It is clear that these kinds of discoveries will contribute to an understanding of health disorders in ethnic minorities and other populations.

INITIATIVES IN MINORITY HEALTH RESEARCH AND TRAINING

Mr. Stokes. What significant initiatives in minority health research and research training, and outreach are supported by your Institute?

Dr. Cassman. As you know, NIGMS programs have been the cornerstone of the NIH's efforts to increase the underrepresentation of minorities in biomedical research and research training for the past 20 years. The Minority Access to Research Careers (MARC) Program provides special research training opportunities for students and faculty at four-year colleges, universities, and health professional schools in which substantial student enrollments are drawn from minority groups. The Minority Biomedical Research Support (MBRS) Program awards grants to educational institutions with substantial minority enrollments to support research by faculty members, strengthen the institutions' biomedical research capabilities, and provide opportunities for students to work as part of a research team. The National Predoctoral Fellowship Program, the Bridges Program, and the Institute's active participation in the NIH Minority Supplement Program, all of which are described above, represent additional significant participation in minority health research and research training initiatives.

With respect to outreach, the Institute supports a Minority Programs Symposium every other year, in which hundreds of students and faculty involved with the MARC and MBRS Programs, and recruiters from majority institutions, are brought together for a scientific symposium. In addition, for the past three years, the Institute has hosted regional workshops designed to assist minority institutions which have not actively participated in the MARC or MBRS Programs to develop competitive applications for one or both of these Programs, or to consider participating in the Bridges Program.

SETTING PROGRAM PRIORITIES

Mr. Stokes. How does your Institute identify its priorities for investments in minority research and research training?

Dr. Cassman. In making its plans and setting priorities, the Institute primarily takes into consideration the views of its advisors, on its Advisory Council and its review committees, the views of representatives of various groups "invested" in minority research and research training, and the ideas of participants in the Institute's various programs. In addition, the recommendations growing out of the 1991 and 1992 work of the NIH Minority Programs Fact-Finding Team and on-going discussions with the Director, Office of Research on Minority Health (ORMH), help shape these plans and priorities.

RELATIONSHIP WITH OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes. When the Office of Research on Minority Health provides funds to your Institute, do these funds typically augment existing minority programs or efforts, or do they replace funds your Institute previously invested in its minority research and research training initiatives. Elaborate.

Dr. Cassman. The funds from the Office of Research on Minority Health augment the Institute's. The vast majority of funds provided to NIGMS by the Office of Research on Minority Health is devoted to the Bridges to the Future Programs initiated by that office, but implemented and administered by NIGMS. While NIGMS funds the staff and overhead expenses to run the Bridges Programs, the Institute does not contribute to the grants funded themselves. The Bridges Programs were begun in 1992 in response to recommendations in the report of the NIH Minority Programs Fact-Finding Team established by the Director, ORMH. The ORMH has also provided varying amounts in each of the last few years to cofund certain grant efforts of the MARC and MBRS Programs and to support some national predoctoral fellowship awards that NIGMS otherwise could not afford to fund.

Mr. Stokes. When your Institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health?

To what extent is there a collaborative relationship between the two organizations. Elaborate.

Dr. Cassman. The Bridges Program is a recent and very fine example of the collegial and collaborative relationship between NIGMS and the Office of Research on Minority Health. While the impetus and funding for the program originated from the Office of Research on Minority Health, most of the details and guidelines regarding implementation, review, and ongoing administration have been handled by NIGMS, with the concurrence of ORMH. This arrangement has worked so well because of the open lines of communication between the two organizational components. We anticipate an enhancement in the already excellent lines of communication between the Institute and ORMH now that the Director of the NIGMS Minority Opportunities in Research Programs, Dr. Clifton Poodry, has joined the Institute.

RESEARCH SUPPLEMENTS FOR UNDERREPRESENTED MINORITIES

Mr. Stokes. I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Cassman. The Research Supplements for Underrepresented Minorities program was first announced in April 1989, five years ago. Through FY 1993, NIH had made a total of 3,302 awards for $111,426,403. Although many of the minority participants, especially at the earlier educational stages (high school, undergraduate, and graduate) are still in training, some, at the upper career levels (postdoctoral fellows and investigators), have begun to achieve some measure of success. For example, in FY 1989, the Program's first year, NIGMS supported one postdoctoral fellow and two investigators. The postdoctoral fellow is presently a Research Associate at Duke University. One of the investigators is on the staff at the Brigham and Women's Hospital in Boston and he has received his own research funds from a non-NIH source. The other investigator is on the staff at the Massachusetts Institute of Technology and Massachusetts General Hospital. While the Institute has only followed up formally on all the candidates supported in FY 1989 (a total of fifteen), on occasion more recent participants report their achievements to us, unsolicited. For example, a candidate supported as a postdoctoral fellow for eighteen months beginning in 1992, at the University of Utah, is now an Assistant Professor of Inorganic Chemistry at the University of Oklahoma.

Since 1989, the NIGMS has supported 66 minority postdoctoral fellows and 21 minority investigators in FY 89-93. To date, none of these has received an NIH research grant.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes. What are some of the major initiatives underway at your Institute to increase the participation of historically black colleges and universities in biomedical research?

Dr. Cassman. In responding to earlier questions, we mentioned the MARC, MBRS, Bridges, National Predoctoral Fellowships, and the NIH Minority Supplement Programs. In addition to these, the Institute has sponsored a regional workshop for the past three years which was designed to assist minority institutions which have not actively participated in the MARC or MBRS Programs in developing competitive applications for one or both of the programs. Institute staff also provide ongoing technical assistance to potential grantees for the MARC, MBRS, and Bridges Programs, and for other initiatives, such as the various fellowship programs.

MINORITY STAFFING IN NIGMS

Mr. Stokes. How many GS-15 and above positions are there in your Institute.

Dr. Cassman. NIGMS has 27 positions at the GS-15 level or above.

Mr. Stokes. How many employees in your Institute are in GS-15 and above positions?

Dr. Cassman. Employees presently occupy 24 of the 27 positions at the GS-15 level or above.

Mr. Stokes. In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they?

Dr. Cassman. Presently African Americans occupy 2 GS-15 level positions, namely the Associate Director for Referral and Liaison, NIGMS, and the Deputy Director, Biophysics and Physiological Sciences Program Branch, NIGMS.

Mr. Stokes. In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Cassman. Presently NIGMS has no requests pending for any exceptions at the GS-15 and above level.

Mr. Stokes. Has the NIH requested relief from the freeze; if so, what was the response?

Dr. Cassman. NIH has held discussions with the Public Health Service about relief from the freeze. The PHS continues to evaluate the status of employment levels to determine whether FY 1994 employment ceilings can be met without continuing the freeze on hiring. To date, that evaluation has not been encouraging enough to have the freeze lifted. Instead, some exceptions to the hiring freeze have been granted.

Mr. Stokes. If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Cassman. Recently, the NIGMS was granted exceptions to the hiring freeze for two candidates, both underrepresented minorities for grants management specialist positions, a FEORP-targeted occupation. These accessions, along with others still in the Merit Promotion process, could enhance the Institute's affirmative employment workforce profile, while bringing to the Institute new staff with considerable talent.

PREVENTION RESEARCH

Mr. Stokes. With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Cassman. The NIGMS supports fundamental science in areas ranging from genetics and structural biology to trauma and burn research. This represents, in its purest form, prevention research. Since an understanding of the fundamental processes of living organisms has been shown to be the most direct route to an understanding of specific disease entities, the research that the NIGMS supports will contribute to the ability to prevent these diseases.

SUPPORT TO MINORITY INSTITUTIONS

Mr. Stokes. What is the present level of support provided to minority institutions by your Institute?

Dr. Cassman. In FY 1993, NIGMS provided $44,119,000 to minority institutions.

Mr. Stokes. Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by Historically Black Colleges and Universities in the Institute's programs and activities.

Dr. Cassman. Historically Black Colleges and Universities have been among those invited to attend the regional technical assistance workshops held during the past few years. Many HBCUs have sent representatives to these meetings and NIGMS has seen some application activity from institutions that participated. In addition, to help enhance the infrastructure at minority institutions, the Institute has done several things:

- increased funding for the Minority Biomedical Research Support (MBRS) Program, which helps develop the research capabilities of minority institutions;
- reannounced the availability of instrumentation supplements to ongoing MBRS grants so that state-of-the-art research instruments will be part of the research infrastructure at those institutions;
- developed and announced a new career development award for faculty at minority institutions to perform summer research or to take coursework to update their research skills;
- modified and reannounced two faculty fellowship opportunities for faculty at minority institutions. These opportunities enable faculty to seek Ph.D. degrees or pursue sabbatical research at research-intensive institutions before returning to their own minority institutions.

Together with programs funded by other components of the National Institutes of Health, these efforts are intended to strengthen the infrastructures of minority institutions.

Mr. Stokes. Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Cassman. In Fiscal Year 1995, the NIGMS proposed budget requests the funding for its various minority programs as follows:

Program	1995 Request (in $000)
MARC	$15,714
MBRS	36,535
National Predoctoral Fellowships	3,449
Other Special Initiatives	738
Minority Supplements	4,711
NIGMS Total	$61,147

Additional funding is expected from the Office of Research on Minority Health to fund the Bridges Program, and contributions from other NIH institutes will supplement the MARC, MBRS, and National Predoctoral Fellowship Programs.

TEAM APPROACH TO AIDS DRUG DESIGN

Ms. Pelosi. Dr. Cassman, in your testimony, you describe the concept of "rational drug design" and suggest that this approach has much promise for new drugs to fight AIDS. However, progress in developing these drugs to date has been slow and disappointing.

As you may know, a group called the Future Directions on AIDS Research or the "Madison Project" has suggested that NIH set aside a small part of the federal AIDS research funds to invest in a research project to demonstrate a more flexible, more team-oriented management for drug development. In your view, are alternative models to research management potentially useful in the AIDS research program, particularly as it relates to filling in the gaps between basic science and AIDS drug development?

Dr. Cassman. To some extent, new models for research management have been tried by NIGMS, with the establishment of a series of interdisciplinary program projects to bring together structural biologists, theoreticians, and medicinal chemists to attempt to "design" drugs effective against potential targets associated with in the AIDS virus. Progress has been modest but encouraging. To date, the three dimensional structure of the enzyme responsible for transforming the information contained in the RNA of HIV to DNA which is incorporated into the host, reverse transcriptase, has been determined by x-ray crystallography and using theoretical methods considerable progress has been made in the design of chemicals to inhibit the protease enzyme responsible for processing HIV proteins.

Beyond this effort, it is worth noting that the main recommendation of the Madison Project was implemented with the establishment of the National Task Force on AIDS Drug Development. At the first meeting held two weeks ago, this Task Force identified the discovery and development of new therapies as the top priority for fighting AIDS. To identify barriers to the discovery of new drugs, a subcommittee of the Task Force will meet over the summer and report back to the entire Task Force at its next meeting in the fall. Alternative models to research management will be carefully considered at the meetings of the subcommittee. A member of the NIGMS staff responsible for the administration of the AIDS training grants and interdisciplinary program projects is working closely with the Task Force and its subcommittee.

WOMEN AND MINORITIES IN RESEARCH

Ms. Lowey. Are we making any progress in raising the share of women and minority researchers in the field? Can you update the Committee on the Institute's role in this effort?

Dr. Cassman. In many fields, both women and minorities face problems of underrepresentation. However, in the biomedical sciences it is minorities and not women who remain significantly underrepresented. Over the 10-year period from 1982 to 1992, the proportion of Ph.D.s in the life sciences earned by women has increased from 30 percent to 44 percent. Currently, women represent more than 40 percent of NIH pre- and postdoctoral trainees and fellows in the biomedical sciences, and more than 60 percent of those receiving pre- and postdoctoral support in the behavioral sciences. The representation of women in research training programs and among research grant recipients also has been steadily increasing over the past decade. There has been some difficulty in retaining women in science careers, particularly during their childbearing years. To address this problem, NIH is now considering changes in its training policies to allow part-time positions on training grants, creating more flexibility in training programs.

A more serious problem for the field has been the underrepresentation of minorities. In 1989, African-Americans, Hispanics, and Native Americans made up only about 3 percent of employed doctorates in the biological sciences, while representing roughly 18 percent of the total U.S. workforce. Over the past decade, there has been a slight increase in the number of minorities receiving doctoral degrees in the life sciences. In 1982, only 3.1 percent of Ph.D. recipients in these fields were underrepresented minorities; in 1992, minorities represented 5.1 percent of the Ph.D. recipients. The goal of existing NIGMS programs is to ensure further and more rapid progress in this area, and new ways are sought continually to meet this critical need.

One component of the NIGMS, the Minority Opportunities in Research (MORE) Programs Branch, serves as the focal point for NIGMS efforts to increase the number and capabilities of minority individuals engaged in biomedical research. The MORE Program, through its various components, provides special training opportunities in the biomedical sciences for students and faculty at institutions with substantial minority enrollments an well as for students seeking the Ph.D. or combined M.D.-Ph.D. in biomedical science. Institutional research capabilities are strengthened through funding faculty and student participation in research at colleges and universities with substantial minority enrollments. The development of new and innovative programs and the expansion of existing programs is encouraged to improve the academic competitiveness of underrepresented minority students, facilitating their transition into the next stage of preparation for careers in biomedical research.

HISPANIC RECRUITMENT AND PROMOTION

Mr. Serrano. Dr. Cassman, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions.

First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Cassman. The National Institute of General Medical Sciences (NIGMS) is committed to increasing the number of Hispanics in positions and grade levels in the work force in which they are currently underrepresented.

In recent years, NIGMS has consistently included in its Affirmative Employment Program (AEP) Plans and Federal Equal Opportunity Recruitment Program (FEORP) Plans, elements to address the underrepresentation of Hispanics in various occupations and grade levels within the Institute. To achieve the goals outlined in the NIGMS AEP and FEORP Plans, the Institute established expanded job vacancy mailing lists that include Hispanic professional organizations, such as the Society for Advancement of Chicanos and Native Americans in Science (SACNAS), and the placement offices of institutions affiliated with the Hispanic Association of Colleges and Universities. In addition, for some positions, the Institute places advertisements in newspapers for metropolitan areas with significant Hispanic populations.

When filling vacant positions, NIGMS has Hispanics serve on committees that are part of the screening process, including search committees and qualifications review boards.

Each year, NIGMS provides funding for staff members to attend the SACNAS Annual Conference. This conference provides an opportunity for participants to network, and to call employment opportunities to the attention of Hispanics in attendance.

SUPPORT FOR HISPANIC HEALTH-RELATED RESEARCH AND TRAINING

Mr. Serrano. Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Cassman. Because of the Institute's mission, NIGMS does not support research targeted on specific diseases or populations. Instead, the NIGMS supports research in a broad range of fundamental disciplines. Findings from this basic research have been shown to have an impact on many diseases. For example, recent reports have demonstrated that the discoveries of NIGMS investigators in areas such as cell division and repair of DNA, lead to the ability to identify and understand the genetic defects in inherited forms of cancer. It is clear that these kinds of discoveries will contribute to an understanding of health disorders in ethnic minorities and other populations.

Mr. Serrano. Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Cassman. NIGMS sponsors a number of programs designed to increase the participation of underrepresented minorities in biomedical research:

> The Minority Access to Research Careers (MARC) Program provides special research training opportunities for students and faculty at four-year colleges, universities, and health professional schools in which substantial student enrollments are drawn from minority groups.
>
> The Minority Biomedical Research Support (MBRS) Program awards grants to educational institutions with substantial minority enrollments to support research by faculty members, strengthen the institutions' biomedical research capabilities, and provide opportunities for students to work as part of a research team.
>
> The National Predoctoral Fellowship Program, initiated in Fiscal Year 1991, awards predoctoral fellowship awards to minority students enrolled in graduate schools throughout the country.
>
> The Bridges Program, initiated in Fiscal Year 1992, was designed to address two problems. First, it was designed to help minority students "bridge" the gap between two-year junior or community colleges and four-year universities. Second, the Program established a bridge between universities granting the Master's degree in Science as the terminal degree and universities granting a doctoral degree.
>
> In addition, NIGMS participates actively in the NIH Minority Supplements Program through which minority investigators, graduate students, postdoctoral students, college students, and sometimes even high school students can be added to the budget of a research grant, to enable them to receive research training, retraining, or to establish research collaborations.

With regard to outreach at the precollege levels, a number of colleges supported by our MARC and MBRS Programs have developed their own community outreach programs in order to interest high school students in attending their institutions to prepare for careers in biomedical research. In addition, a number of Institute staff are very active in the NIH Science Alliance Program. This program takes NIH scientists to Washington, D.C. metropolitan area schools, primarily elementary schools, to provide "hands-on" science instruction and experiments. It is hoped that these experiences will intrigue more young people into pursuing careers in science and research.

HISPANICS IN CLINICAL TRIALS

Mr. Serrano. Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Cassman. Because its mission is the funding of basic biomedical research, the NIGMS does not sponsor clinical trials.

GRANTS TO HISPANIC INVESTIGATORS

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Cassman. In FY 1993, the overall success rate for research grant applications in NIGMS was 29.6 percent; for applicants who identified themselves as Hispanic, it was 27.0 percent. However, the overall numbers of applications from Hispanic investigators was small. Of the 2,620 grant applications received by NIGMS, 35 applications were from Hispanics and 10 grants were awarded. The Institute awarded 780 research grants in FY 1993.

WEDNESDAY, APRIL 20, 1994.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

NATIONAL INSTITUTE OF DRUG ABUSE

NATIONAL INSTITUTE FOR NURSING RESEARCH

WITNESSES

ANTHONY S. FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

ALAN I. LESHNER, PH.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

ADA SUE HINSHAW, PH.D., R.N., NATIONAL INSTITUTE OF NURSING RESEARCH

Mr. SMITH. Okay. We will get started. We have got a bad afternoon ahead of us. Votes every 10 minutes. We have three more of the Institutes this afternoon. Allergy and Infectious Diseases, Drug Abuse, and Nursing Research. Dr. Varmus.

INTRODUCTION OF WITNESSES

Dr. VARMUS. This is Dr. Anthony Fauci, the Director of the National Institute of Allergy and Infectious Diseases and Dr. Alan Leshner, the new Director of the National Institute on Drug Abuse, and Dr. Ada Sue Hinshaw, who is the Director of the National Institute for Nursing Research.

Mr. SMITH. Thank you. Go ahead.

OPENING STATEMENT

Dr. FAUCI. Mr. Chairman, I would like to take a few minutes to describe for you some of the activities of the National Institute of Allergy and Infectious Diseases. As you know, much of what we do in the NIAID relates either directly or indirectly to AIDS research.

As you are probably aware, over the last several months there have been reports on the increase in heterosexual transmission of HIV in the United States which, in fact, has led to an increase in the number of cases among women and children born to HIV-infected women.

In this regard, I want to bring to your attention what we regard as a major advance in therapeutics. As shown here in figure 1, there was a study reported in the newspapers a month ago about the use of AZT in HIV-infected pregnant women that decreases the transmissibility from the mother to the infant from about 25.5 percent to 8.3 percent.

Dr. Varmus mentioned this to you in his opening statement as one of the several, but one of the top three that he mentioned, important areas of research. This finding will have an extraordinary health care cost savings since we project that there will be a possible prevention of 1,000 infected children's births per year.

Closely related to our work on HIV is the portfolio on sexually transmitted diseases research. Figure 2 displays the major segments of this area from basic research up through and including vaccine development. Also we have intensified and interwoven our biological interventions with behavioral interventions. This linkage is an important component of our STD research. Furthermore, we are collaborating with the Child Health Institute on a topical microbicides initiative with the goal of reducing not only sexually transmitted diseases, but all HIV transmissibility, since when you have ulcerative genital diseases in women and men there is a five times greater chance of transmitting HIV.

In addition, topical microbicides are an important tool that will empower women in protecting themselves from the transmission of HIV and other STDs. With regard to the whole concept of prevention research, as depicted here in Figure 3, the NIAID is heavily involved in basic and clinical vaccine research. First, we develop vaccines for diseases for which we have no effective vaccine such as asthma, malaria and others. Second, we develop vaccines in areas in which there is toxicity, such as pertussis, and third, we improve vaccines by reducing the number of shots or administrations that are needed by developing more potent vaccines with or without an adjutant.

Let me move on to mention another area of increasing interest and importance: chronic fatigue syndrome. We feel that this is a real disease. It is very problematic because the criteria for determining the presence of the disease is still in its formative stages. As shown here in Figure 4, we have an increasing number of investigation initiatives as well as program solicited research predominantly at the extramural level, and we have had very good interaction over the last year with the constituency groups involved with the chronic fatigue syndrome and the coordinating committee at the Department.

Dr. Philip Lee is actively involved in the CFS coordinating committee and we are pleased that we are going in the right direction with this important disease.

Tuberculosis is another important disease. Figure 5 compares the trend of where we should have been with TB by the end of 1992: from a little bit over 25,000 cases per year down to below 10. As a result of the HIV epidemic, we have shifted from a plateauing in the 1980s to an increase in the 1990s because the immune system of HIV-infected individuals has been destroyed. A strong immune system is the body's protective mechanism that keeps TB latent.

Compounding this problem has been the development of multiple drug resistant tuberculosis, which is a very important and problematic situation with regard to health care workers, prison guards, and people in clinics, and the homeless shelters who take care of HIV-infected individuals.

Lyme disease is another important emerging microbe. There are more than 10,000 cases per year in this country and it has emerged as the most important vector-borne disease in the United States. Figure 6 shows the Borrell, an organism, that causes Lyme disease, which is transmitted by a tick bite and was discovered by an NIAID scientist. We have a comprehensive effort dealing with treatment, vaccine and diagnostics, but most importantly is the intensification of our effort to determine the relationship of therapy to chronic persistent disease which has become a persistent problem in more than 48 States in the Union.

Let me close with a look towards the future. NIAID-supported researchers over the past year or two have been successful in isolating and identifying what we call the stem cell, shown here in figure 7, which is the cell that is the origin of all blood cells in the body, platelets, red blood cells: cells of the lymphoid system.

The reason this is important is that this will lead to breakthroughs in the areas of bone marrow transplantation, reconstitution of the blood system and the lymphoid system in individuals with acquired immunodeficiency, the treatment of cancer, and a variety of other immune deficiency diseases. I would hope that I could come back to this Committee over the next several years and give you progress reports about this very important area of research.

This concludes my formal statement, Mr. Chairman. I would be happy to answer any questions later.

[The prepared statement of Dr. Anthony Fauci follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Allergy and Infectious Diseases

The developed world today enjoys a level of public health higher than at any previous time in history, largely due to the availability of vaccines, antibiotics, sophisticated diagnostic tests and other technologies. Some of the accomplishments of this century have been remarkable: smallpox has been eradicated through worldwide vaccination efforts, and polio has been virtually eliminated in the western hemisphere. In the past decade at least nine new or improved vaccines have become available.

Despite these extraordinary successes, however, many challenges to our Nation's health remain. The human immunodeficiency virus (HIV) and its associated complications continue to devastate the lives and families of men, women and children, especially in our inner cities. In recent months, infectious organisms have compromised the water supplies in several of our cities. Drug-resistant strains of pathogens, such as those that cause tuberculosis (TB), now elude once-effective therapies. Sexually transmitted diseases (STDs) are widespread, especially among our young people. Obscure microbes have emerged to cause serious outbreaks of disease, such as the Hantaan virus seen in the southwest United States. Asthma rates have risen among minority children in our cities. The number of people needing organ transplants, especially in minority populations, is rising each year.

These trends emphasize that the mission of the National Institute of Allergy and Infectious Diseases (NIAID) -- preventing, diagnosing and treating infectious diseases and disorders of the immune system -- is more vital than ever. The research programs at NIAID, which range from basic studies of the immune system to behavioral interventions, reflect the Institute's mandate to reduce the burden of disease in both human and economic terms. Underpinning these efforts is the work of basic researchers: bench scientists working toward a better understanding of the biology of microbes, how they invade the body and cause disease, how the immune system responds, and what responses are protective. A detailed understanding of the immune system is especially critical to understanding immunologically mediated conditions such as asthma, allergies, the rejection of transplanted organs, and the acquired immune deficiency syndrome (AIDS).

NIAID's research programs hold special promise for helping minorities and women, who bear a disproportionate burden of certain conditions. In the inner city, people of color suffer rates of infectious diseases such as TB, HIV infection and sexually transmitted diseases far higher than the population as a whole. End-stage kidney disease, with the resulting need for a kidney transplant, is four times more prevalent in African-Americans than in whites. Autoimmune diseases are six times more common in women than in men. Research into the prevention or treatment of all of these conditions falls under the purview of the NIAID.

Vaccines are the public health tools that offer the greatest potential to reduce death, illness and health-care costs. NIAID-supported researchers are developing new classes of vaccines to protect individuals from acquiring viral, bacterial, parasitic and fungal infections, and employing biotechnology to improve older vaccines that are based on weakened or killed microbes. NIAID also contributes to the research component of the Children's Vaccine Initiative, a global program to develop safe and effective vaccines.

HIV infection is spreading throughout the world at an alarming rate. According to various estimates, 40 to 110 million people could be infected with HIV by the year 2000. The development of a vaccine that would prevent HIV infection or HIV disease is a national and international health priority. NIAID is pioneering the development of HIV vaccine candidates by employing new genetic engineering and molecular biology technology. At the same time, the Institute is establishing the infrastructure for conducting large-scale clinical trials as soon as suitable candidate vaccines are identified.

Traditionally, live, attenuated or weakened viruses have proven to be the most effective vaccines. Promising results have been obtained recently with an experimental vaccine that protected monkeys against an HIV-like retrovirus known as simian immunodeficiency virus (SIV). The vaccine was created by deleting one SIV gene. Attenuated SIV vaccines are now being constructed with four or five genetic elements deleted, thus providing an extra margin of safety. If these prove to be safe and effective in monkeys, similar approaches may be cautiously pursued in man.

For those already infected with HIV, it is crucial to develop therapies that prolong and improve the quality of life. In the past year, studies conducted by NIAID researchers have increased our knowledge of the multifactorial, overlapping processes that enable HIV to progressively weaken the immune system. This information is being used in the development of comprehensive treatments directed at a number of different disease mechanisms, particularly those that occur during the early phase of infection, when the virus spreads rapidly throughout the body.

The study of HIV infection in women is a major focus of NIAID research. We recently initiated a large-scale project to study the signs and symptoms of HIV infection in women, describe the pattern and rate of their immune system decline and examine potential co-factors that may affect their disease progression. This knowledge is vital to the design of research projects and clinical trials to evaluate better treatment strategies. The study also is enrolling uninfected women at high risk for HIV infection, providing data on the risk factors for infection and on the effectiveness of initiatives to prevent HIV infection in women.

HIV-infected women give birth to about 7,000 babies each year in the United States, and approximately 25 percent of these infants become infected with the virus before or during birth. Recently, investigators demonstrated that AZT given to HIV-infected pregnant women can reduce by two-thirds the risk of transmission of HIV to their newborns. Further study will help determine the risks and benefits of the treatment beyond these encouraging early results.

Each year, an estimated 10 to 12 million Americans acquire an STD other than HIV disease. Approximately 65 percent of these infections occur in people under 25 years of age, with 3 million cases among teenagers. These infections, which frequently occur without symptoms, are often unknowingly passed to others and can cause serious complications, especially in women as well as in children born to infected women. Moreover, the risk of becoming infected or infecting others with HIV is much higher when someone has another STD such as herpes, syphilis, gonorrhea or chlamydial infection.

Because of the urgency of the STD epidemic, initiatives to prevent and control STDs are a key priority of NIAID. Important progress is being made in the areas of vaccines, diagnostics, therapy, behavioral interventions and other methods that promise to facilitate the prevention of STDs and HIV infection.

Recently, NIAID-funded research has led to simple tests for vaginitis and chlamydial infection. NIAID scientists have also developed an experimental vaccine for chlamydial infections that shows promise in laboratory tests. Such a vaccine has the potential to reduce the more than 4 million chlamydial infections that occur each year and the associated costs, which exceed $2.4 billion annually.

NIAID is also funding research to test the potential of microbe-killing chemicals that could be used in the vagina to protect women from STDs, including HIV, and prevent the spread of STDs to their sexual partners.

Partly because of the HIV epidemic, the health threat posed by TB has resurfaced; since 1985 the number of active cases in the United States has risen by 20 percent. In response to the resurgence of TB, NIAID has formulated a comprehensive research agenda. Priorities include studies on the basic biology of the disease as well as initiatives to develop new and improved TB vaccines, better diagnostic tools, new and improved drug treatments, and improved modes of drug delivery.

The rapid diagnosis and successful treatment of TB are vital for both the patient's welfare and for limiting the development and spread of drug-resistant strains of the organism. In the past year, researchers supported by NIAID reported an experimental technique that holds promise for speeding the diagnosis and ultimately the treatment of TB.

Lyme disease is another growing threat to the Nation's health. More than 9,000 cases were reported in the United States in 1992, up from only a few hundred prior to 1984. In

NIAID laboratories and at grantee institutions, scientists are intensively studying the bacterium that causes Lyme disease and how it interacts with the immune system to thwart the body's defenses and cause disease. This basic research is essential to developing improved diagnostics, treatments and vaccines.

Researchers have shown that vaccines based on a Lyme bacterium surface protein can protect mice from infection; several of these vaccines are in various stages of clinical trials. Investigators also have identified a number of immune-activating proteins from the bacterium, with an eye toward improving the accuracy of existing diagnostic tests for acute and chronic Lyme disease. Recently, NIH-sponsored researchers have used a sensitive technique called polymerase chain reaction (PCR) to detect the bacterium in joint fluid, providing a method to confirm whether a patient's arthritis is the result of active Lyme infection that could be treated with antibiotics.

Chronic fatigue syndrome (CFS) is a puzzling illness characterized by unexplained, debilitating fatigue, flu-like symptoms, and cognitive complaints. Earlier this year, NIAID investigators reported that CFS patients have higher proportions of certain white blood cells bearing markers indicative of chronic stimulation; hypotheses to explain this observation are currently being tested. Investigations at NIH also suggest that a hormonal imbalance may help explain the lethargy associated with CFS. A study is now under way to determine if low-dose hydrocortisone can restore the hormonal levels to normal and alleviate CFS symptoms.

For many of those affected with kidney failure and other chronic diseases, the transplantation of an organ or tissue is not only life-saving, but, when successful, restores a good quality of life to patients. However, immunologic rejection of organs is a major barrier to successful transplantation. An important area of study focuses on ways to improve upon the currently available methods for treating and preventing rejection, which cripple the entire immune system and make the patient susceptible to infection and cancer. Scientists have shown, in monkeys, that it is possible to induce donor-specific tolerance so that the animals can tolerate transplanted kidneys without the need for lifelong treatment with immunosuppressive drugs. Such studies may have clinical applications in human transplantation.

Allergies, which affect 40 to 50 million Americans, are the sixth leading cause of chronic disease in the United States. Major scientific discoveries by NIAID-supported scientists have contributed significantly to our understanding of allergic disease, including asthma, and have led to substantially better methods of diagnosing and treating them. NIAID-funded scientists were the first to identify the IgE antibody that is the key to the allergic response, and have now identified the complex structure of the receptor on allergy-causing cells to which IgE antibodies attach. The receptor provides a promising target for drugs that might block allergic reactions at their outset.

Despite our best efforts to prevent and control infectious diseases and immune disorders, changes in microbes and our environment will surely present new challenges. The speed with which new and improved vaccines, diagnostic tests, drugs and other measures can be developed will depend on our understanding of the human immune system and the ever-growing array of pathogenic invaders that threaten human health. With today's knowledge and modern technologies at our disposal, extraordinary advances in disease prevention are possible. NIAID's continued investment in biomedical research, from basic science to clinical trials and behavioral studies, will provide important benefits to the health of this and future generations.

Mr. Chairman, the FY 1995 budget request for this Institute is $542,864,000. I will be pleased to answer any questions you may have.

FAUCI, DR. ANTHONY S.
Director, National Institute of Allergy and Infectious Diseases

December 24, 1940. Brooklyn, New York

Education:

College of Holy Cross, 1962 - A.B.; Cornell University Medical College, 1966 -M.D.

Professional History:

1966-1967, Intern, Department of Medicine, New York Hospital-Cornell Medical Center. 1967-1968, Assistant Resident, Department of Medicine, The New York Hospital-Cornell Medical Center. 1968-1970, Clinical Associate, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland. 1970-1971, Senior Staff Fellow, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1971-1972, Chief Resident, Department of Medicine, New York Hospital-Cornell Medical Center; Instructor in Medicine, Cornell Medical College. 1972-1974, Senior Investigator, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1972-present, Consultant in Infectious Diseases, The National Naval Medical Center, Bethesda, Maryland. 1974-1980, Head, Clinical Physiology Section, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1977-1984, Deputy Clinical Director, NIAID, NIH, Bethesda, Maryland. 1980-present, Chief, Laboratory of Immunoregulation, NIAID, NIH, Bethesda, Maryland. 1984-1988, Clinical Professor, Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Georgetown University School of Medicine, Washington, D.C. 1985-1988, Clinical Professor, George Washington University School of Medicine and Health Sciences, Washington, D.C. 1988-1994, Director, Office of AIDS Research, NIH, and Associate Director of NIH for AIDS Research, Bethesda, Maryland. 1984-present, Director, NIAID, NIH, Bethesda, Maryland.

Board Certification and Military Service:

American Board of Internal Medicine-June 21, 1972. American Board of Allergy and Immunology-March 1, 1974. American Board of Infectious Diseases-October 15, 1974. U.S. Public Health Service, July 1968-June 1970; July 1972-Present.

Professional Organizations:

American Federation for Clinical Research, American Association for the Advancement of Science, American Association of Immunologists, American Medical Association, Fellow of the American Academy of Allergy, Infectious Diseases Society of America, American Society for Clinical Investigation, Fellow of The American College of Physicians, Member, Association of American Physicians, Fellow of the Collegium Internationale Allergologicum, Charter Member of the Clinical Immunology Society, International AIDS Society, American Society for Virology, Fellow of the American Academy of Arts and Sciences, Member of the Institute of Medicine of the National Academy of Sciences (USA), Foreign Member of the Royal Danish Academy of Sciences and Letters, Member of the National Academy of Sciences (USA).

Offices Held:

Councillor, Eastern Section, American Federation for Clinical Research (AFCR), 1977. National Councillor, AFCR, 1978-1979. President, AFCR, 1980-1981. Recorder, Association of American Physicians, 1988-1993. Councillor, Association of American Physicians, 1993-present.

Advisory Boards and Committees:

Chairman, Allergy and Immunology Committee, MKSAP V, American College of Physicians. Advisory Panel, The American Board of Medical Laboratory Immunology. Member, Committee on Clinical Immunology and Immunopathology, American Association of Immunologists, 1980-1985. Representative of American Association of Immunologists to the Examinations Committee of the American Board of Allergy and Immunology, 1981-present. Postgraduate Education Committee, American Academy of Allergy, 1979-1982. Member, NIAID Study Group on Immunology, 1980. Member, Section of Physiology in Clinical Science of the American Physiological Society, 1980-1984. Member, Subcommittee on the Classification of Vasculitis, American Rheumatism Association 1980-present. Ad Hoc Committee, The National Foundation for Infectious Diseases, 1980-present. Subcommittee on Clinical Sciences, Publications Committee, American Physiological Society, 1980-1984. American Association of Immunologists, 1982-1985. Member, NIAID Working Group for AIDS, 1982-present. Member, American Federation for Clinical Research President's Public Policy Advisory Committee, 1983-present. Board of Directors, American Board of Allergy and Immunology, 1984-1987. Participant in the USA - People's Republic of China Immunology Cooperative Agreement, August 1983, Beijing and Shanghai, PRC. Member, Scientific Advisory Board, Medical Biology Institute, La Jolla, CA, 1983-1984. Participant in the USA-Japan Eye Immunology Advisory Conference, November 1983, Honolulu, HI. Member, External Advisory Committee, Multipurpose Arthritis Center, Duke University Medical Center, 1984-present. Member, Honorary Advisory Board, Italian-American Medical Association, 1984-present. Member, Peripatetic Club, 1984-present. Ex Officio Member, National Diabetes Advisory Board, 1984-present. Ex Officio Member, National Digestive Diseases Advisory Board, 1984-present. Chairman, Search Committee for Director, National Institute of Child Health and Human Development, 1985. Member, Department of Health and Human Services Task Force on Alzheimer's Diseases. The Albert Lasker Medical Research Award Jury, 1985-present. Deputy Ethics Counselor, Department of Health and Human Services, 1985-present. Member, Department of Health and Humans Services Committee to Coordinate Environmental and Related Programs, 1985-present. Member, Scientific Organizing Committee, Joint Meeting of the Italian Society of Immunology and Immunopathology-National Institutes of Health on "Human Lymphocyte Activation," Florence, Italy, September 1985.

Member, United States Delegation to the United States-Japan Cooperative Medical Science Committee, 1985-present. Member, U.S. Public Health Service AIDS Executive Task Force, 1985-present. Chairman, NIH AIDS Executive Task Force, 1985-present. Coordinator, NIH AIDS Research, 1985-present. Member, Scientific Seminar Subcommittee, National Institutes of Health Centennial Program, 1985-1987. Member, Advisory Board, Clinical Immunology Newsletter, 1986-1988. Member, Scientific Organizing Committee, International Conference on Lymphocyte Activation and Immune Regulation, Newport Beach, CA, February 1986. Member, Planning Committee, Clinical Immunology Society, 1986. Member, International Advisory Committee, International Conference on AIDS, Paris, France, June 1986. Member, Advisory Group, Institut Scientifique Roussel-Uclaf, 1987-1989. Ex Officio Member, National Kidney and Urologic Diseases Advisory Board, 1987-present. Member, International Programme Committee, 8th International Congress of Immunology, Budapest, Hungary, 1987. Member, International Advisory Committee,IVth International Conference on AIDS, Stockholm, Sweden, June 1988. Member, NIH Resource Allocation Group, 1987-1989. Member, Committee for the Coordination of Research Programs on the Acquired Immunodeficiency Syndrome of the Ministry of Health of Italy, 1988-present. Institute of Medicine Roundtable for the Development of Drugs and Vaccines Against AIDS, January 1989-December 1993. Member, Selection Committee for the National Public Service Awards, 1990.

Editorial Boards:

Dr. Fauci has been or is on the Editorial Board of 28 scientific journals in the field of immunology, allergy and infectious diseases. These include: The Journal of Clinical Investigation, The Journal of Immunology, Journal of Infectious Diseases, Journal of Clinical Immunology, The Journal of Experimental Medicine, The New England Journal of Medicine. Dr. Fauci is also the Editor of one of the major textbooks of medicine in the world, "Harrison's Principles of Internal Medicine."

Awards and Honors:

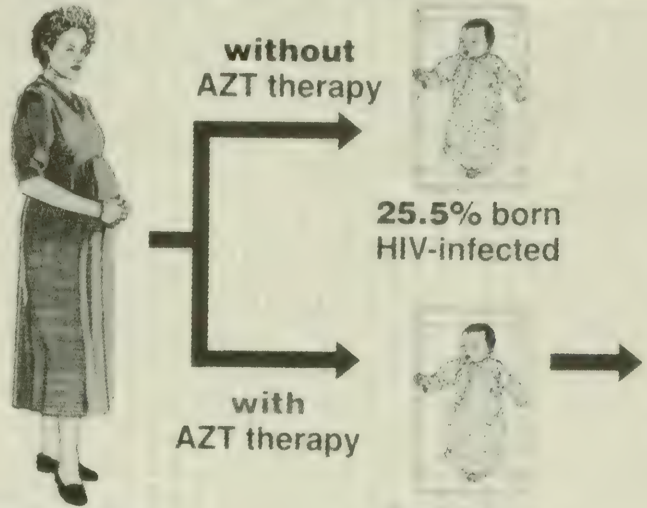
Alpha Omega Alpha. Kileen Prize for Excellence in Chemistry (College of the Holy Cross). John Metcalfe Polk Prize for General Efficiency (Cornell University Medical College). Alfred Mortitz Michaelis Prize for Efficiency in General Medicine (Cornell University Medical College). U.S. Public Health Service Meritorious Service Award, 1979. Arthur S. Flemming Award, 1979 - Given to the 10 outstanding employees in the U.S. Federal Government. Squibb Award of the Infectious Diseases Society of America, 1983. U.S. Public Health Service Distinguished Service Medal, 1984. Food and Drug Administration Commissioner's Special Citation, 1984. 1985 Citation Classics (Current Contents) for article - A.S. Fauci, D.C. Dale, and J.E. Balow: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann. Intern. Med. 84: 304-315, 1976. Who's Who in America, 44th Edition. Who's Who in Science and Technology, 2nd Edition. 1985 Stanford University Center Survey of the American Rheumatism Association membership ranked the work of Dr. Anthony S. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the past 20 years. The Clemens von Pirquet Award of Georgetown University Medical Center, 1986. Doctor of Science, Honoris Causa, College of the Holy Cross, Worcester, MA, May 1987. The Kober Lecture Award of the Association of American Physicians, 1988. Public Health Leader of the Year Award of the Commissioned Officers Association of the U.S. Public Health Service, 1988. The National Institutes of Health Clinical Center Annual Distinguished Clinical Educator Award, 1988. 1988 Citation Classics (Current Contents) for article - A. S. Fauci, B. F. Haynes, P. Katz: The spectrum of vasculitis. Ann. Intern. Med. 89: 660-676, 1978. The Leadership Award of the Columbus Citizens Foundation, Inc., for "Inspired Leadership and Outstanding Achievement in the Field of Medical Research," New York, NY, October 1988. American Association for the Advancement of Science/Westinghouse Award for Public Understanding of Science and Technology, 1988. The National Hemophilia Foundation Special Award for Research in AIDS, 1989. The Lee P. Brown National Public Service Award of 1989 presented by the National Academy of Public Administration and the National Society for Public Administration. The Duke University Award for Rheumatologic and Immunologic Research, 1989. The William Beaumont Award of the American Medical Association, 1989. The academic Excellence Award from Children's Hospital National Medical Center, Washington, DC, 1989. The Surgeon General's Exemplary Service Medal, 1989. The Surgeon General's Medallion, 1989. The 1989 Achievement Award of the American Association of Physicians for Human Rights. The 1989 National Medical Research Award of the National Health Council. The Flame of Hope Award of the Terri Gotthelf Lupus Research Institute, November 1989. The 1989 Maxwell Finland Award in Infectious Disease presented by the National Foundation for Infectious Diseases. The 1989 Helen Hayes Award for Medical Research. The Excellence in Public Service Award of the Committee for the Support of Public Service, May 1990. The 1990 Lifetime Science Award of the Institute for Advanced Studies in Immunology and Aging, Washington, DC. Doctor of Science, Honoris Causa, Mount Sinai School of Medicine, New York, NY, May 1990. Doctor of Science, Honoris Causa, Neumann College, Aston, PA, May 1990. Doctor of Science, Honoris Causa, Georgetown University School of Medicine, Washington, DC, May 1990. Doctor of Science, Honoris Causa, Hahnemann University Graduate School and School of Medicine, Philadelphia, PA, June 1990. 1990 Science Citation Index ranked Dr. Fauci as the eighth most-cited scientist among 1.3 million scientists publishing in the time period 1981-1988. 1990 Humanitarian Award of the Human Rights Campaign Fund Federal Club of Houston. The First International Chiron Prize for Biomedical Research awarded by the Scuola Superiore di Oncologia e Scienze B Biomediche (Genoa) and the Scuola Internationale di Oncologia e Medicine Sperimentale (Rome), 1990. Doctor of Medicine and Surgery, Honoris Causa, Universita di Roma, "La Sapienza," Rome, Italy, 1990. The Fifth Annual Gene Frey Memorial Award for Medicine, The Whitman-Walker Clinic, Washington, DC, November 1990. The 1990 Presidential Award of the New York Academy of Sciences. Fellow, American Academy of Arts and Sciences, 1991. Doctor of Science, Honoris

Causa, St. John's University, Jamaica, NY, May 1991. Honorary Fellowship, The New York Academy of Medicine, March 1991. The Award of Courage from the American Foundation for AIDS Research for "extraordinary leadership and personal scientific contributions to AIDS research," December 1991. 1991 Institute for Scientific Information Database Analysis indicated that of the more than 1 million scientists in the world who published in the decade 1981-1990, Dr. Fauci was the 2nd most cited (Nature 355: 101, 1992). Foreign Member, Royal Danish Academy of Sciences and Letters, 1992. Elected to the National Academy of Sciences (USA), 1992. 1992 Sidewalks of New York Science Award from the Big Brothers/Big Sisters of New York City, Inc., New York, May 1992. Establishment of the Anthony S. Fauci, M.D. Perpetual Scholarship by the Sons of Italy Foundation, May 1992. The Cornell University Medical College Alumni Award of Distinction, May 1992. Doctor of Science, Honoris Causa, Long Island University - Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Brooklyn, NY, June 1992. Honorary title of "Il Commendatore della Repubblica" conferred by the President of the Republic of Italy, June 1988. Election to Fellow, American Association for the Advancement of Science. The Thomas H. Ham - Louis R. Wasserman Award of the American Society of Hematology, December 1992. The Department of Health and Human Services Secretary's Certificate of Appreciation for "Outstanding contribution in the implementation of the parallel track initiative of the U.S. Department of Health and Human Services," January 1993. The 1992 Dr. Nathan Davis Award for Outstanding Public Service. Awarded by the American Medical Association to a "Member of the Executive Branch of the Federal Government in Career Public Service." Visiting Professor of Medicine at a large number of major medical schools throughout the country. The Department of Health and Human Services Secretary's Certificate of Appreciation for "Outstanding contribution in the implementation of the parallel track initiative of the U.S. Department of Health and Human Services," January 1993. The 1992 Dr. Nathan Davis Award for Outstanding Public Service. Awarded by the American Medical Association to a "Member of the Executive Branch of the Federal Government in Career Public Service." The Howard University Outstanding Achievement Award, 1993. 1993 Citation Classics (Current Contents) for article - H. C. Lane, H. Masur, L. Edgar, G. Whalen, A. H. Rook, and A. S. Fauci: Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N. Engl. J. Med. 309: 453-458, 1983. Doctor of Science, Honoris Causa, Medical College of Wisconsin, Milwaukee, WI, May 1993. The R. E. Dyer Lectureship Award, National Institutes of Health, May 1993. Doctor of Science, Honoris Causa, Bard College, May 1993. Doctor of Science, Honoris Causa, Bates College, May 1993. The Humanitarian Award of the Tiro a Segno Foundation, 1993. The Cartwright Prize of Columbia University College of Physicians and Surgeons, New York, NY, November 1993.

Publications:

Dr. Fauci has authored over 800 scientific publications in the field of basic and clinical immunology and infectious diseases.

AZT Reduces Rate of Maternal Transmission of HIV



HIV-infected
mother

without
AZT therapy

25.5% born
HIV-infected

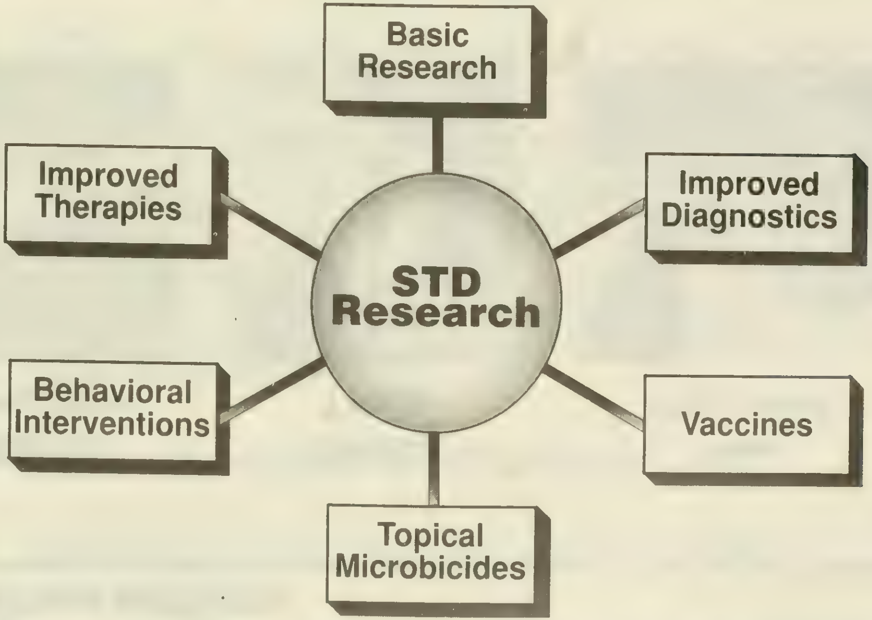
with
AZT therapy

8.3% born
HIV-infected

Possible prevention of 1200 infections/year in U.S.

Figure 1.

NIAID Sexually Transmitted Diseases Research



STD Research

Basic Research

Improved Diagnostics

Vaccines

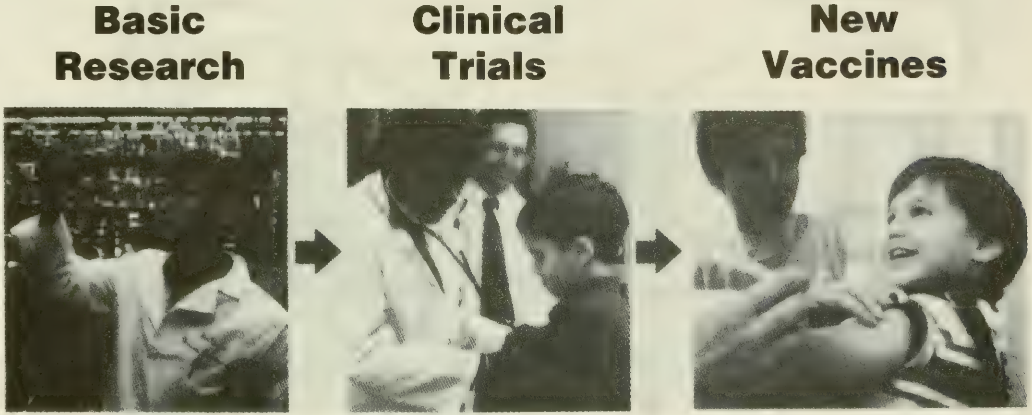
Topical Microbicides

Behavioral Interventions

Improved Therapies

Figure 2.

NIAID Vaccine Research: A Formula for Prevention



Basic Research

Clinical Trials

New Vaccines

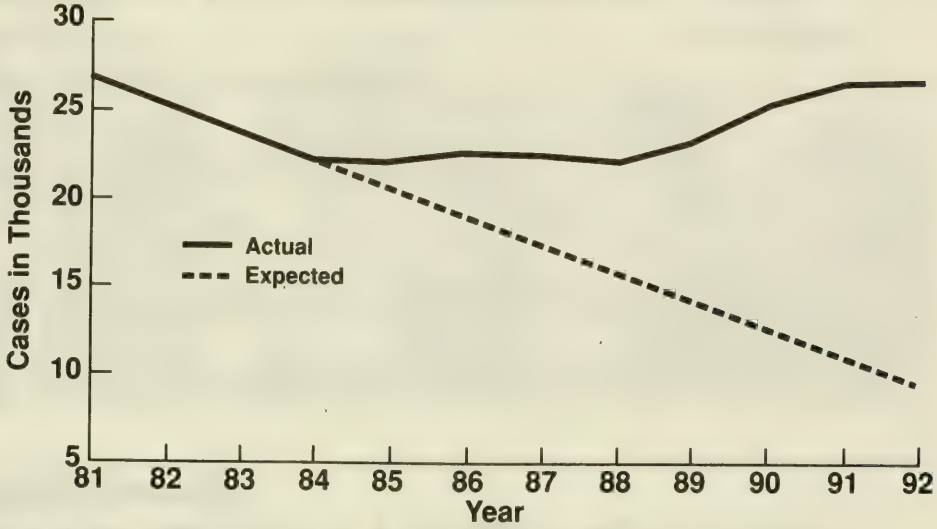
Figure 3.

NIAID Chronic Fatigue Syndrome Research

- 3 CFS Cooperative Research Centers (CRC)
- 11 pilot projects supported through CRC program
- 10 extramural grants
- Intramural Research
- Clinical Management Workshop
- Interactions with constituency groups

Figure 4.

Actual Versus Expected Tuberculosis Cases in United States, 1981-1992

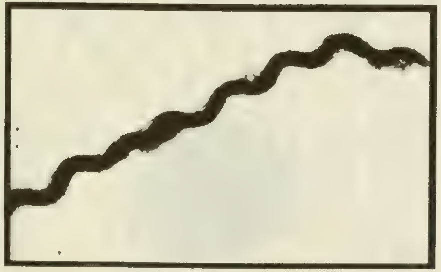


Lyme Disease

10,000 cases in 1992

New Diagnostics

Treatment Research



Acute vs Chronic Disease

Vaccine Development

Figure 6.

Stem Cells: Origin of All Blood Cells

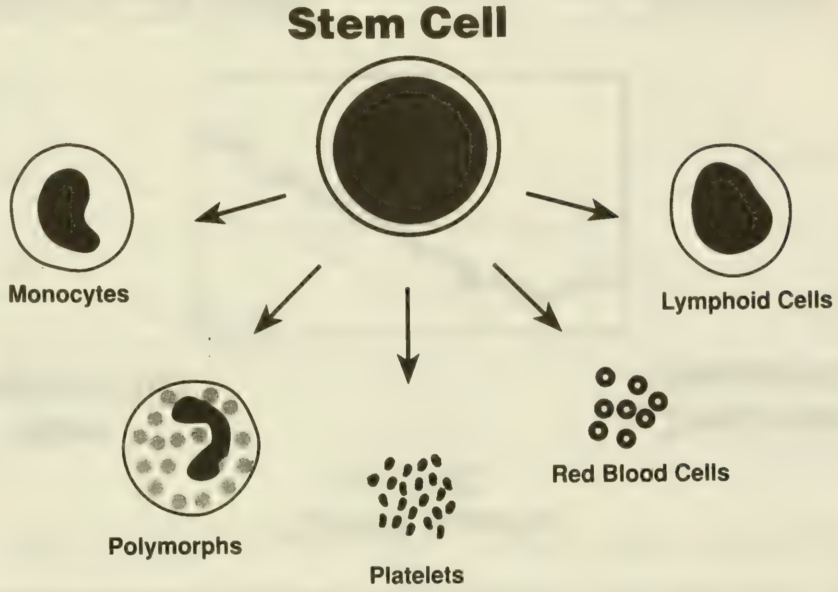


Figure 7.

Mr. SMITH. Dr. Leshner.

OPENING STATEMENT

Dr. LESHNER. Thank you, Mr. Chairman. It is both an honor and a pleasure to have the opportunity to testify before this committee for the first time as the Director of the National Institute on Drug Abuse. NIDA is celebrating its 20th anniversary this year and I am its fourth director.

I have come to NIDA at a particularly opportune time because the past five years have seen truly extraordinary discoveries that provide unique and exciting opportunities to significantly improve drug abuse prevention and treatment. Some of these advances have resulted from the application of newly available biomedical technologies. Others have come from advances in the behavioral and social sciences. In many cases what we are seeing is the natural transition and use of basic research findings in clinical and applied research and then into the practice community.

Given the complexity of the issues of drug abuse and addiction, we at NIDA need to bring to bear the techniques of many, many disciplines on this important social and public health problem. Those disciplines range from the most molecular approaches to the behavioral and social sciences. We are fortunate that we have been making great strides in all of these arenas with both interesting scientific and useful practical implications.

As a first example, NIDA researchers have made great progress in mapping the complex brain reward mechanisms involved in drug addiction. All major drugs of abuse appear to exert their rewarding mechanisms on the same brain system. Moreover, NIDA researchers have identified and genetically specified receptors in the brain for every major drug of abuse. We now know at the whole brain level and at the cellular level where drugs of abuse are working in the brain.

Applications for tools of molecular biology have also been teaching us a great deal about how drugs work on the brain. We are learning now how those receptor effects, for example, can change cell function. And, of course, different drugs act on different areas of the brain and in somewhat different ways, although there is substantial overlap among drugs of abuse which might account for some of their common properties.

Knowing how and where drugs work in the brain is not just intellectually interesting, which it is; it also is particularly important, because for the first time it provides us an opportunity to begin what we would call rational medication design to produce treatments that will block or vaccinate against the effects of drugs like heroin and cocaine.

There is widespread agreement, particularly articulated by a recent study from the Institute of Medicine that medications development has to be the essential focus of this country's attack on drug abuse.

I want to change tacks just a little bit and move from the more biological approaches to the problem to comment on some of the things that have happened from epidemiologic research on drug abuse and addiction. We have had 20 years of epidemiologic research, and it has told us a great deal about the risk factors and attitudes that make individuals vulnerable to abusing drugs. As with complex social problems, many of those risk factors are indeed daunting. In fact, many are factors that NIDA cannot impact directly.

Because we can't impact them directly, NIDA is taking another approach to the whole epidemiologic set of issues as well. In the midst of every drug epidemic and in the face of multiple risk factors there are many individuals who remain drug free, who don't become drug abusers in spite of having many of those risk factors. We are working hard to identify exactly what those protective factors are. And, of course, that kind of knowledge will allow us to develop new kinds of prevention strategies that try to help us understand why in the face of multiple risk factors, many individuals don't become drug abusers, and perhaps we can generalize from that. This is a somewhat different approach than we have used historically.

Let me turn to the issue of drug treatment because it is also extremely complex. We all know that drug addiction treatment can and does work for many of those people who are willing to enter treatment, and such interventions are overall cost-effective. One of the things we have to do is convey this information more effectively to drug abusers and their families and give them the message that help is available.

However, even though we have therapies that work for some people, these programs require a long commitment to treatment and don't work for everyone. The dropout rates, the relapse rates, are terrifying. Treatment matching studies are one important need. Individual differences and preferences, individual differences in the kinds of treatments that people will respond to, are an important focus. In addition, we have to learn to increase the efficiency as well as the effectiveness of treatment.

Building on some other comments that have been made in another related domain, drug abuse of course will continue to fuel the AIDS epidemic unless we take the necessary steps to improve both the prevention and treatment of addiction. Almost a third of all new cases of AIDS are related one way or another to intravenous drug use. Drug addiction treatment is an effective AIDS prevention strategy. For example, NIDA researchers have demonstrated that participation in methadone treatment does reduce HIV seroconversion rates and does, in fact, decrease high-risk behavior. Contrary to popular belief, intravenous drug abusers can and will change their HIV risk behaviors. We have had a variety of outreach strategy studies over the course of the last 10 years and have mounted another multisite study. These previous outreach studies have shown substantial declines in the use of potentially contaminated syringes and changes in sexual behavior, as well.

Finally, I think it is important not to forget drug abuse's devastating impacts on children. In the AIDS arena about 56 percent of pediatric AIDS cases are drug abuse-related. Critically important are additional studies of mother to infant HIV transmission and pediatric progression of HIV disease, as well as appropriate outreach and treatment studies for pregnant women. Generally, we need to focus far more attention to the problems drug abuse causes for our Nation's children. Babies born to addict parents suffer medically. Children raised in drug abusing households suffer emotionally and adolescents who abuse drugs suffer the risk of ruining their lives. Studying the effects of drug abuse from infancy to adolescence will become a major NIDA priority.

Thank you. I will be happy to answer any questions.

[The prepared statement and biography of Dr. Alan Leshner follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

STATEMENT OF ALAN I. LESHNER, PH.D.
DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

Mr. Chairman and members of the Subcommittee, I am pleased to come before you as Director of this superb NIH Institute and to review some of our accomplishments and plans. NIDA sees its principal mission as bringing the full power of science to bear on what to many believe is our Nation's most pressing public health and social problem, drug abuse and addiction. We then take that scientific information and work to ensure its rapid application in both real-life medical practice and health policy settings.

NIDA was created in 1974 with the conviction that drug addiction, like cancer and heart disease, is a complex illness that can be addressed by scientific research. This approach has allowed us to make some truly exceptional advances in understanding, treating and preventing drug addiction. The accomplishments of the past decade, and especially the past few years have been nothing short of extraordinary and these accomplishments form the basis for our expectations for accelerated progress in addressing the problems of drug abuse. For example,

- We have now identified and genetically specified the molecular sites in the brain where every major drug of abuse has its initial effect. These discoveries, together with computer-aided drug design, should enable us to rapidly synthesize novel compounds to break the cycle of addiction.
- We have identified endogenous opiate systems in the brain that are involved in addiction, pain, and other diseases and physiological functions.
- We have identified the brain receptors for the active ingredient in marijuana, Δ^9 - tetrahydrocannabinol, and have discovered endogenous brain chemicals that act on these receptors.
- We worked to develop methods and standardized procedures for analyzing urine, hair, and meconium for signs of drug exposure. These technologies are invaluable in workplace drug prevention programs and for forensic purposes.
- We defined the addictive nature of nicotine, its similarities to cocaine, and the role that cigarette smoking plays as a risk factor for drug abuse.
- We have also enhanced our abilities to treat drug exposed children, measure the extent of drug abuse in various populations, treat cocaine abuse using behavioral techniques, measure the abuse potential of new drugs, specify the neurotoxicological effects of drugs, and use methadone and other interventions to help prevent HIV.

NIDA researchers also continue to investigate the prevalence of drug abuse among our children through our annual survey of high school students. Drug abuse can destroy the lives of children and adolescents and our recent surveys indicate that this problem is not going away. Our studies have confirmed the common sense view that as the perceived risk of using drugs goes up, the use of drugs goes down; that was the pattern for most of the past decade. Unfortunately, the most recent data show that the perceived risk has decreased and use has increased. These findings raise concern and reinforce the notion that we must continue to provide information about the risks of drug use and learn how to further emphasize the social norms that oppose drug use.

A particularly exciting accomplishment for NIDA during 1993 was the approval of a new medication for the treatment of heroin addiction. LAAM, 1-alpha-acetyl methadol, is the first new medication for the treatment of heroin since methadone was approved over 20 years ago. LAAM's main advantages are that it has a long duration of action and needs to be administered only three times per week, thereby reducing clinic visits, and it appears to have limited abuse liability, thereby cutting down on illicit diversion.

NIDA is moving forward with a number of new and exciting medications for drug addiction. We recently completed safety studies of a long acting form of the opiate antagonist naltrexone. This dosage form can provide up to 30 days of opiate blockade, preventing heroin abuse during this period. Additional medications under development for opiate addiction include buprenorphine, which combines the best attributes of methadone and naltrexone in a single medicine, and other compounds that will make it easier to medically withdraw addicts from drugs.

NIDA is also supporting efforts to develop medications to treat cocaine and crack abuse. With the recent cloning of the gene for the dopamine transporter, one of the prime brain sites at which cocaine acts, the time is ripe to develop medications that can block the action of cocaine. This will be a daunting task but scientists at NIDA's intramural research program at the Addiction Research Center have identified some novel compounds that, hopefully, will inhibit the action of cocaine on the brain reward system without destroying the ability of an individual to experience drug free natural pleasures.

NIDA research has demonstrated that treatment can work. However, we need to improve techniques to recruit and retain patients in treatment and prevent relapse. We are also finding that multi-component preventive programs, such as school-based interventions, supported by parent education and community-wide media campaigns, are more likely to be effective in reducing drug use, compared to more limited approaches. Additional research is needed to identify protective factors such as effective parenting.

Through its National AIDS Demonstration Research Program, NIDA is also demonstrating that outreach programs can significantly alter behaviors associated with the spread of AIDS associated with drug use. This program is also determining the most effective interventions in different communities.

These discoveries, and those of the past two decades, have provided us with unprecedented insights into, and new technologies to study, the actions of drugs in the brain and the cascade of events which contribute to addictive behavior. It is critical that we build on these findings by continuing to support, and indeed expand support, for research in promising areas.

New technologies have provided us with a realistic view of the brain mechanisms underlying drug reward and euphoria. Ten years ago our understanding of the brain circuitry involved in reward could be represented by a simple cartoon (Fig.1). A diagrammatic representation (Fig.2) of our current understanding of the brain's reward system shows a highly complex series of brain areas and neuronal interconnections. Advanced techniques, such as the capability to simultaneously study the activity of several hundred neurons, are also allowing us to gain new insights into how individual neurons in these areas are involved in addiction. This has already provided a comprehensive view of neural activity in the brain reward system related to drug self-administration. This more realistic view of the brain will ultimately help us develop more realistic approaches to prevention and treatment.

It is clear that molecular biology and neuroscience are two of the most exciting areas of drug abuse research in which NIDA needs to expand support to take advantage of recent advances. The cloning of the genes for the receptors for each of the major drugs of abuse, for example, provokes new questions and new thinking about drug actions and brain function. Specifying the location of these genes as part of the Human Genome Project, determining specific biological vulnerabilities of drug addiction, and the possibility of gene-based therapies for drug addiction are but a few of the exciting opportunities.

The complex relationship between behavior and biology in drug use can also be more fully explored using advanced technologies, such as neuroimaging. For example, new techniques can monitor the neuropsychological status of an awake subject while viewing a computerized image the brain. Such technologies may dramatically increase our understanding of the biological bases of craving, drug-seeking behavior, euphoria, drug tolerance, drug dependence, and drug addiction, and should be extremely useful for the development of effective therapies. These technologies will also allow us to determine whether pharmacological and/or behavioral interventions will reverse neurobiological and neurochemical changes caused by drug use. Such changes are seen in Fig. 3 which shows that even after three months of cocaine abstinence, the brain of a former cocaine addict is still functioning abnormally.

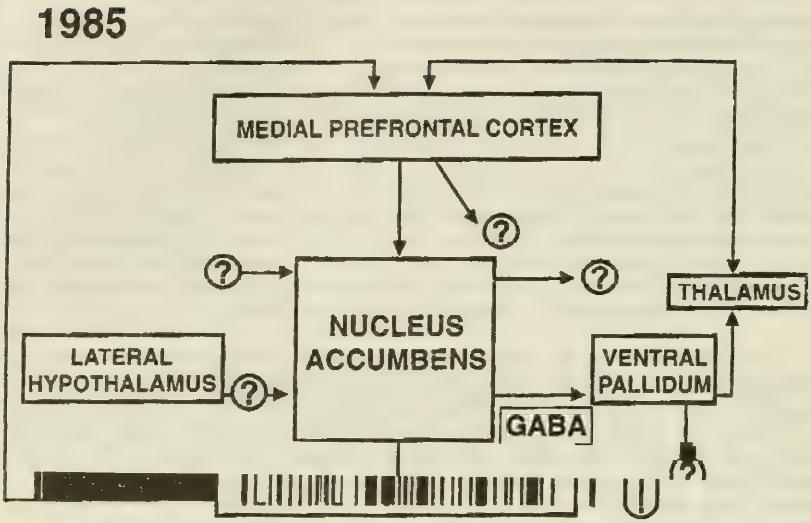
We also anticipate substantial progress in the development and refinement of psychosocial and behavioral therapies for the treatment of drug addiction. NIDA is launching the Behavioral Therapies Development Program which will build upon knowledge gained from basic behavioral and clinical studies to define, develop, and refine behavioral therapies, including behavioral interventions, psychotherapies, counseling approaches, and other rehabilitative strategies.

NIDA's health services research program also promises opportunities for important progress. NIDA views research on drug abuse treatment and prevention services, the linkage between drug abuse and the primary health care system, and HIV/AIDS prevention services research as major components of our research program. This comprehensive, multidisciplinary approach to drug abuse health services research is necessary because of the unique characteristics of drug abuse clients, the range of needs they present, the changes in health care organization, financing, and utilization which are taking place, and the need to understand how and why some clients respond to prevention and treatment while others are resistant to engagement and change. Future health services research will build on the existing knowledge base and focus on areas relevant to prospective changes in health care organization, financing, and utilization.

NIDA will continue to support research in other areas as well, including studies to develop integrated and comprehensive pharmacologic and behavioral treatments; studies of the effectiveness of prevention programs; investigation of the natural history of drug abuse and its consequences, including diseases associated with drug abuse, such as AIDS and tuberculosis; clarification of behavioral issues that impact getting drug users into treatment, retaining them there, and preventing relapse; and studies of the developmental problems which may result from maternal drug use. Equally important are efforts to expedite the transfer of information between providers and researchers.

Mr. Chairman and members of the committee, the rapid advances made in the fields of neuroscience, molecular biology, and sophisticated behavioral science research together with the many accomplishments in other areas of drug abuse research, now provide us with a base from which to take advantage of unparalleled opportunities to address the problems of drug abuse. We have an opportunity to improve primary health care, reduce infant mortality, promote mental health, advance health care for women and minorities and the underserved, and prevent and treat HIV infection and tuberculosis through drug abuse research. NIDA's overall objective is to improve our understanding of drug abuse and related problems and to develop more effective interventions. We must continue our present research efforts and, in line with the President's budget, we should expand our efforts in the several most promising areas I have noted.

Thank you Mr. Chairman. I would be pleased to answer any questions.


1985
MEDIAL PREFRONTAL CORTEX
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THALAMUS
NUCLEUS ACCUMBENS
LATERAL HYPOTHALAMUS
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VENTRAL PALLIDUM
GABA
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Figure 1

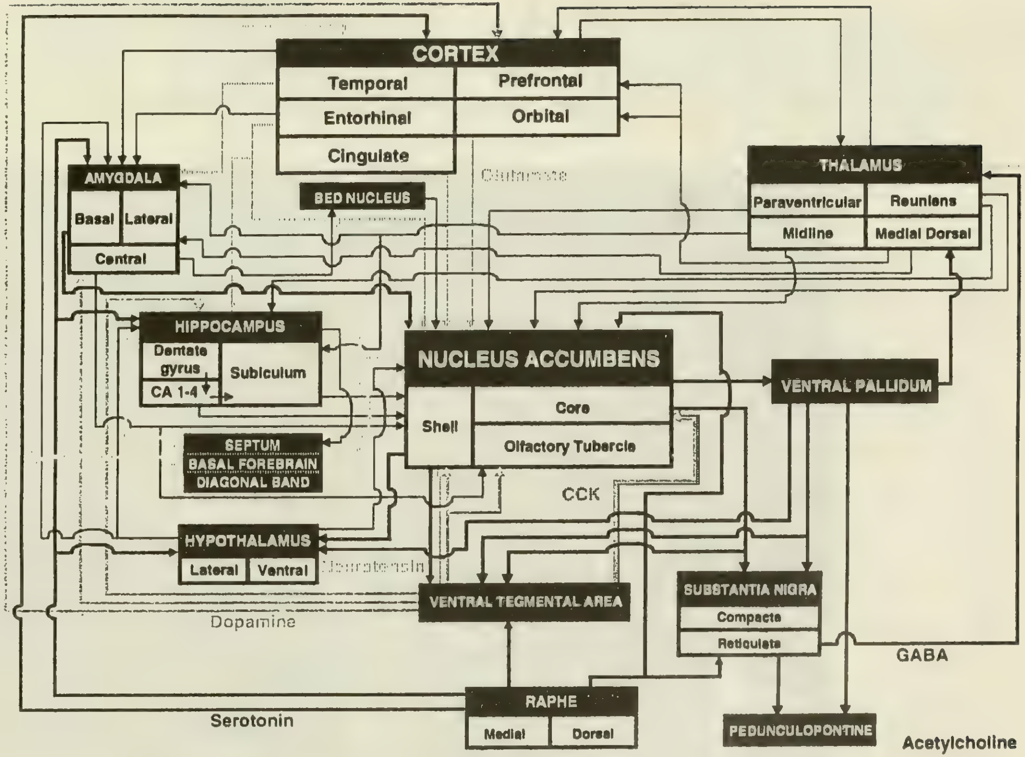

Figure 2 Schematic of Drug Brain Reinforcing Systems

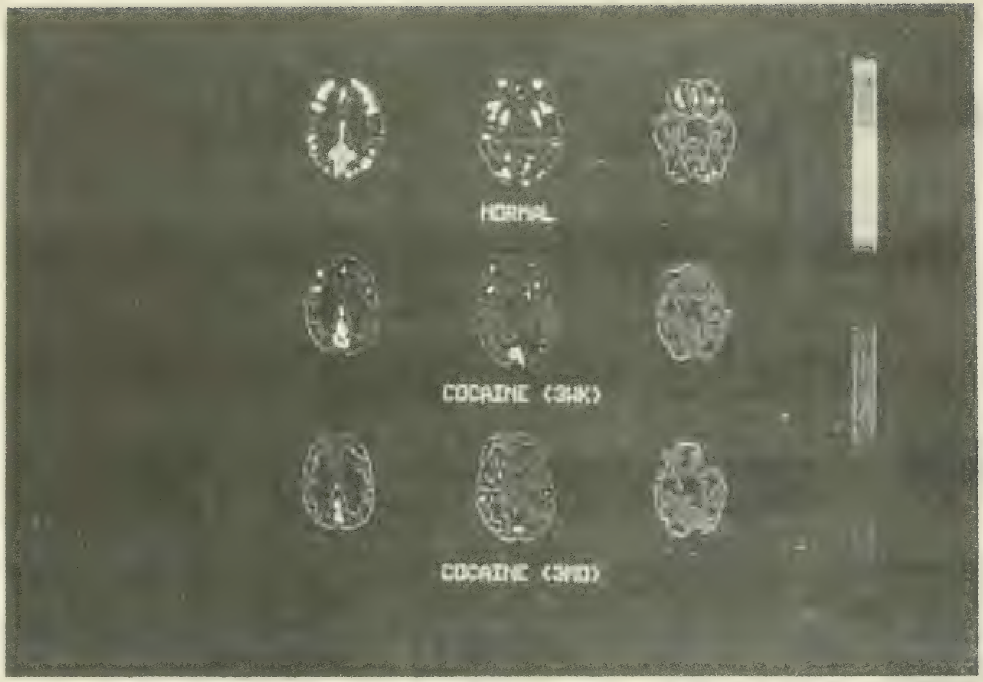

Figure 3 Brain glucose metabolism for a normal control and a cocaine abuser tested 3 weeks after detoxification and again after 3 months of detoxification. The images were obtained using 18F-deoxyglucose and PET. Slide presents three levels of the brain of a normal subject and of a cocaine abuser.

ALAN I. LESHNER, PH.D.
Director, National Institute on Drug Abuse
National Institutes of Health

Dr. Leshner was appointed Director of the National Institute on Drug Abuse in February 1994. Prior to that appointment, he served as Deputy Director of the National Institute of Mental Health since 1988, where he also served as Acting Director from 1990 to 1992.

Among his accomplishments have been a major restructuring of the priorities and programs of the National Institute on Mental Health to greatly enhance treatment research, a set of programs to build the mental health field's clinical research infrastructure, and strategic plans to advance health services research. He also has provided leadership in the development of major national resources, like the Human Brain Project, and in articulating and developing the basic neuroscience and behavioral science portfolios of NIMH. He was appointed by the Secretaries of HHS and HUD as Chair of the task force that produced Outcasts on Main Street, which lays out a blueprint for substantially reforming the national system of care for homeless persons with severe mental illnesses and substance abuse, and he was involved in the President's Health Care Reform Task Force.

Previous to his work at NIDA and NIMH, Dr. Leshner held a broad variety of positions at the National Science Foundation (NSF). He was Director of the Office of Science and Technology Centers Development, responsible for a Foundation-wide program to develop and support major research centers around the country across all fields of science and technology. Before assuming that position, Dr. Leshner had been deputy to the NSF Assistant Director for Biological, Behavioral and Social Sciences. He served in numerous other positions at NSF, including overseeing the National Science Board (NSB) Commission on Precollege Education in Mathematics, Science and Technology, one of the two national commissions of the early 1980s that brought renewed attention to the nation's severe problems in elementary and secondary education.

Dr. Leshner went to NSF after 10 years at Bucknell University where he was Professor of Psychology. While on the faculty at Bucknell, he also held long-term visiting appointments at the Postgraduate Medical School in Budapest, Hungary, at the Wisconsin Regional Primate Research Center of the University of Wisconsin, and as a Fulbright Scholar at the Weizmann Institute of Science in Israel. Dr. Leshner's research has focused on the biological bases of behavior. His laboratory's work emphasized the role of peptide and hormone effects on appetitive behavior, motivation, learning and memory, and such social behaviors as aggression and submission. He is the author of a major text on the relationship between hormones and behavior, An Introduction to Behavioral Endocrinology, and numerous book chapters and papers in professional journals. He also has published extensively in the areas of science and technology policy and education.

Dr. Leshner received his undergraduate degree in psychology from Franklin and Marshall College, and the M.S. and Ph.D. degrees in physiological psychology from Rutgers University. He has been elected a Fellow of the American Association for the Advancement of Science, the American Psychological Association, the American Psychological Society, and the New York Academy of Sciences. He has received awards for his national leadership from such diverse groups as the American Psychiatric Association, the National Alliance for the Mentally Ill, the American Psychological Association, the American Academy of Child and Adolescent Psychiatry, the National Mental Health Association, and the National Prevention Coalition. is the author of a major text on the relationship between hormones and behavior, An Introduction to Behavioral Endocrinology, and numerous book chapters and papers in professional journals. He also has published extensively in the areas of science and technology policy and education.

Mr. HOYER. Thank you very much, Doctor. I think the most efficient way for us to operate is for me to go vote now and take a slight break and then Mr. Smith and Mr. Porter will be back and they will ask questions and I will get back and that will probably be the quickest. We will be right back.

[Recess.]

Mr. SMITH. Go ahead.

OPENING STATEMENT

Dr. HINSHAW. Thank you, sir.

Mr. Chairman, I am pleased to be here today particularly because I can speak for the first time about the programs of the National Institute of Nursing Research. We appreciate the tremendous support you and the Congress have given us, support that made it possible last year for us to become an Institute.

As a representative of NIH's newest Institute, it may be useful for me to review our antecedents before discussing our scientific accomplishments. Congress created the National Center for Nursing Research, which was established at NIH in 1986, and then was redesignated as an Institute in 1993. The goal was and is to provide a strong scientific base for nursing practice within the mainstream of research at the NIH.

NURSING RESEARCH VS. MEDICAL RESEARCH

Nursing research and medical research are highly collaborative, tackling many of the same or similar problems from different perspectives and emphases. Generally speaking, while our medical colleagues focus on diagnosis and treatment of diseases, nurse researchers focus on how people react to illness and its treatment, physically and psychologically, and, therefore, how nurses can intervene to improve the patient and family's adaptation and coping.

Let me illustrate this with a real-life example. Medical scientists focus, for example, on finding better ways to diagnose and treat HIV infection—or which drugs and what doses are best to combat such infection. Nurse scientists approach the HIV issue from another angle, studying the symptoms patients are experiencing, such as eating problems, muscle wasting or fatigue, to determine how these symptoms can be reduced to improve the patient's independence, functional status and quality of life. The collaborative findings of both medical and nurse scientists converge to promote the patient's optimal health.

To elaborate further, nursing research emphasizes studies that promote health and prevent disease and address clinical practice environments—how improvement of nursing care settings and systems influence patients' health outcomes.

We have come a long way in a very short time. And while it is true that the NINR is still small, we are encouraged that our nursing research community is expanding. They are energetic and certainly creative. Nursing research truly represents a rapidly growing area of science for good health, capable of making important contributions to bolster the increasing responsibilities of the nursing discipline—responsibilities certain to expand under health care reform.

PREVENTION OF HIP FRACTURE

Now I would like to discuss some aspects of our science—preliminary findings that show promise in the near future.

A study to reduce the impact of falls of our senior citizens has produced a pad worn at the hip joint, that may prevent fracture of the hip, which happens to about 250,000 people each year. Wearing pads to prevent injuries is not new, particularly to any football fan. The concept of pads that absorb and redistribute the impact of collisions or falls while protecting the bones underneath has been adapted for use by older people who are at high risk for such falls.

Let me show you one of the these pads. You can see the pad is quite thin. Only about 5/8 to 3/4 of an inch thick. It is about the size of two dollar bills put together. Early testing of the pad shows promise that it is able to redistribute the force on a fall into the soft tissues of the hip, and therefore to break the fall's impact on the trochanter, or the head of the femur. The problem has been that people have not been willing to wear the pad.

The first pads were 12 inches long and about 10 inches wide. They were very cumbersome and bulky, and refinements had to be made so that they could be worn within the garment. I will show you the garment. It goes on and off with Velcro, and the hip pads are placed in pockets on each side.

What we have found, working with older people now that the pad has been refined and is smaller is that we are able to get subjects to wear them for 75 to 80 percent of their waking hours. The next stage of the study is to test it the pads for efficiency in helping to prevent fractures from older people's falls.

PREVENTION OF NAUSEA WITH CHEMOTHERAPY

Let me shift gears now. The prevalent treatment for cancer, chemotherapy, causes nausea and vomiting in three out of every four patients even when antinausea drugs are used. These side effects are serious in that they stop patients from continuing therapy and hamper the fight of the disease.

An NINR-funded study builds on a behavioral intervention that is quite effective in reducing the incidence and severity of nausea and vomiting. What is really important is that the investigator has begun to understand those factors that will allow us to predict the patients who are at high risk for nausea and vomiting, so that as the chemotherapy is given, we can work ahead of time to prevent such problems.

HEALTH PROMOTION AMONG YOUNGER CHILDREN

Turning from preliminary findings to talk about current and future endeavors, I would like to mention some principal areas of emphasis. We want to expand knowledge about influences in childhood that will later affect the way that young people make healthy or risk-taking behaviors.

As we know, any of us who are parents, it is usually in the preteen and the teen years when risky behaviors surface. But researchers are in the dark about how teen health habits are shaped by these early childhood experiences, and what can be done to manipulate the childhood factors so that health-promoting and not risk-taking behaviors develop. We also need to know more about how younger children can govern certain biological predispositions, such as weight gain or the ability to control stress. How can we help them avoid the future consequences of smoking or drugs? The Institute wants to build on our current health promotion studies with adolescents to find answers to these and other questions for younger children.

COMMUNITY-BASED HEALTH CARE

A notable strength in the nursing research base is studies at the community level that target health care issues of special populations, such as rural residents, minorities, or people particularly vulnerable to disease. The diverse beliefs and experiences of people of different ethnic and cultural backgrounds are integral to developing health care interventions. For example, we are supporting research that develops and tests behavioral management techniques for rural caregivers of people with Alzheimer's disease. We are supporting development of culturally sensitive prenatal care programs for Hawaiians, Japanese, and Filipino women. And the first priority of Phase 2 of the National Nursing Research Agenda, the Institute's long-range plan, is the theme of community-based health care research for vulnerable, underserved, inner-city and rural minorities.

WOMEN'S HEALTH RESEARCH

To conclude, I want to speak a minute about the expanding area of women's health research. In 1995, an emphasis will be placed on symptom management associated with medical treatment for breast cancer, as well as on normal symptoms typically experienced by women in mid-life, such as hot flashes, insomnia and gastrointestinal problems.

HEALTH CARE REFORM

In addition to these initiatives, the continuing and future direction for the Institute, and indeed for the Nation, is health care reform. Let me give you an example of a study that ties in nicely with the twin health care goals of improved quality and reduced cost. The study was planned and conducted collaboratively by physicians and nurse midwives in order to redefine practice to maintain quality and lower cost for prenatal, labor, delivery, and postpartum care for women with low-risk pregnancies.

Preliminary results indicate many similarities in the care provided by physicians and midwives, but also some differences. The nurse midwives used more low-tech interventions, such as psychological support, education, monitoring the patient through observation, listening, and more frequent checks. Hospital stays were shorter, maternal morbidity was lower, patient satisfaction was higher, and the mother's total charges were almost 10 percent lower with nurse midwifery care.

In closing, as I reflect on nursing research at NIH, I am proud to have been in on the creation and to have seen the growth in size and relevancy of nursing science in addressing the Nation's most pressing health issues. Thank you, Mr. Chairman.

[The prepared statement and biography of Dr. Ada Hinshaw follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Nursing Research

Mr. Chairman, I am pleased to be here today, particularly because I can speak for the first time about the programs of the National Institute of Nursing Research. We appreciate the tremendous support you in Congress have given us--support that has made possible our becoming an Institute at the NIH.

At this stage in our short history, the Institute is building on its scientific foundation, which has already begun to produce findings for nursing practice and to suggest important next steps in furthering scientific knowledge for better health.

I would like to begin by discussing preliminary findings that show promise in the near future. A study of newborns' sucking patterns, for example, may provide a window into the developing brain of very low birthweight babies and help predict neurobehavioral damage. As this chart shows, when we compare sucking patterns of premature infants with those of full-term infants, we see a dramatic difference. The preterm infant's sucking patterns are short, frequent bursts of sucking, whereas the full-term infant's patterns show bursts of longer duration, indicating, among other things, efficiency in consuming more milk. After following infants for six months, there was evidence of the ability to predict their developmental progress based on their initial sucking patterns.

Moving from the very young to older people, a study to reduce the impact of falls of our senior citizens has produced a pad, worn at the hip joint, that may prevent fracture of the hip, which happens to 250,000 people each year. The cost is high, both in human terms--24% die within a year, and monetarily--$7 billion annually. As you can see, the pads are quite thin, yet they are believed to be capable of dispersing the force of a fall and avoiding fracture. The pads are inserted into side pockets of a garment that holds them into place over the hip joints. Engineering these hip pads, however, was not a straightforward process. Originally the pads were much thicker and larger, but in the testing phase older people thought they were bulky and difficult to wear under their clothes. Women in particular thought the pads made them look too heavy. With these thinner, more efficient pads, the compliance trend has gone up, with the study group wearing them 75 to 80% of their waking hours. Still, there are some compliance inhibitors to be overcome to assure greater success, such as difficulties with cognition and dementia.

A prevalent treatment for cancer, chemotherapy, causes nausea and vomiting in as many as 3 of every 4 patients, even when antinausea drugs are used. These side effects are serious in that they can cause patients to stop therapy and severely hamper their fight of the disease. Cancer-fighting drugs do not address the patient's expectations of being sick, whereas systematic desensitization techniques are effective in reducing patient's preconceptions and adverse response to both chemotherapy and antinausea drugs. An NINR-funded study builds on a behavioral intervention that is quite effective in reducing the incidence and severity of nausea and vomiting. The investigator has found a way to predict who is at high risk for these side effects. As cancer progresses and drugs become more potent to combat it, the in-tandem behavioral therapy is realigned to counteract the possibility of progressively severe reactions.

Turning from preliminary findings to four areas that the Institute would like to channel ongoing and future research, we want to expand knowledge about influences in childhood that affect later healthy or risk taking behaviors. We want to know more about how to relieve the symptoms of HIV infection and its treatment and improve patients' quality of life. We want to continue to develop interventions at the community level that are culturally sensitive and that focus on populations that are particularly vulnerable to diseases or risky behaviors. And we want to continue to address women's health issues, such as breast cancer.

Although pre-teen and teen years are when risky behaviors often surface, researchers are in the dark about how teens' health habits are shaped by their early childhood experiences and what can be done to manipulate these childhood precursors so that health promoting, and not risk taking behaviors develop. How can we help children govern certain biological predispositions, such as weight gain, or ability to control stress? How can we help them avoid the future consequences of smoking or drugs? What can health practitioners do to promote positive parental influences in the child's early years, or assess and correct psychological factors, such as poor self esteem, before they lead the child into trouble? The Institute wants to build on current health promotion studies with adolescents to find answers to these questions. Right now we are funding studies to reduce risk factors for cardiovascular disease through education or aerobic exercise; assess the effect of mother-child interactions to the child's behavior and sense of control; and compare children who were either low birthweight or full-term infants to assess their later health, success in school, and behavioral and cognitive competencies. But we need to know more about how the environment, together with biological and cognitive characteristics, affect the child's later selection of risk-taking and health promoting behaviors.

As to the future directions of our intramural program, which we believe to be a showcase for successful collaborative efforts with other institutes, I would like to focus on our HIV studies. We are collaborating in this case with the National Institute of Allergy and Infectious Diseases and are studying interventions to alleviate symptoms and improve the quality of life for AIDS patients. Currently there is a focus on nutritional changes, which make the appetite very temperamental, and muscle weakness during treatment regimens. This year research will be expanded to focus on such issues as fatigue and specific coping factors for maintaining quality of life, despite the downhill course of the illness. A new extramural initiative leading to large-scale clinical studies will include non-drug strategies to ease physical symptoms and investigation of why patients respond differently to symptoms and treatments.

A notable strength in the nursing research base is studies at the community level that target health care issues of special populations, such as minorities, or people particularly vulnerable to disease. The diverse beliefs and experiences of people of different ethnic and cultural backgrounds are integral to developing health care interventions. For example, we support research that develops and tests school-based interventions that lower cholesterol levels in high risk children; culturally-sensitive prenatal care for Hawaiian, Japanese and Filipino women; and special health care support for low-income African American women who are at risk for premature labor. The FY 1995 priority of the National Nursing Research Agenda, the Institute's long-range plan, reinforces the theme of community-based health care research for the vulnerable, the underserved, the inner city and rural minorities. Our focus will be on primary, rehabilitative and convalescent therapies.

I want to just mention that women's health research, another strength of the Institute, will also continue to expand its base of studies, with emphasis in FY 1995 on management of symptoms associated with medical treatment for breast cancer, as well as on symptoms typically experienced by women in mid-life, such as hot flashes, insomnia, and gastrointestinal problems.

Another future direction for the Institute and, indeed, the nation, is health care reform. Let me give you two examples of studies that tie in nicely with the twin health care goals of improved quality and reduced cost. One study compared cost savings and clinical outcomes of patients who were chronically critically ill and were in either the hospital's regular intensive care unit or a special intensive care unit managed by nurses. Preliminary findings indicate that in the special unit, the patients' mortality and morbidity rates were lower, their satisfaction was higher, and their costs were about 7% less. Another study was planned and conducted by nurse-midwives and physicians in order to redefine practice to maintain quality and lower costs of prenatal, labor, delivery and postpartum care. Preliminary results indicate many similarities but also some differences in approach. The nurse midwives used more low-tech interventions, such as psychological support and monitoring the patient through observation and listening, rather than through equipment and drugs. Further, hospital stays were shorter, maternal morbidity was lower, patient satisfaction was higher, and total charges were almost 10% lower for the mother.

In closing, as I reflect on eight years of nursing research at NIH, I am proud to have been in at the creation and to have seen the growth in size and relevancy of nursing science in addressing the nation's most pressing health issues.

Thank you, Mr. Chairman. The FY 1995 budget request for this Institute is $48,326,000. I will be pleased to answer any questions you might have.

Ada Sue Hinshaw, Ph.D, R.N.
Director, National Institute of Nursing Research

May 20, 1939. Arkansas City, Kansas.

Education:

B.S., University of Kansas, Lawrence, Kansas, 1961;
M.S.N., Yale University, New Haven, Connecticut, 1963;
M.A., University of Arizona, Tucson, Arizona, 1973;
Ph.D., University of Arizona, Tucson, Arizona, 1975.

Professional History: 1963-1965, Instructor and Chairperson, Maternity Nursing Section, University of Kansas, Lawrence, Kansas. 1966-1967, Assistant Professor, School of Nursing, University of California, San Francisco, California. 1968-1971, Administrative Coordinator, First Year Undergraduate Program, School of Nursing, University of California, San Francisco, California. 1971-1975, Masters' and doctoral studies, University of Arizona, Tucson, Arizona. 1975-1987, Liaison Position: Director of Nursing Research, University Medical Center, Tucson, Arizona and Professor and Director of Research, College of Nursing, University of Arizona, Tucson, Arizona. 1987-Present, Director, National Institute of Nursing Research, National Institutes of Health.

Professional Organizations: American Academy of Nursing, American Nurses' Association (ANA), ANA Council of Nurse Researchers, Arizona Nurses' Association, Sigma Xi, Western Society for Research in Nursing, Sigma Theta Tau, National Academies of Practice, Institute of Medicine

Honors, Awards: Kay Schilter Award, University of Kansas School of Nursing, 1961. Lucille Petry Leone Award, National League for Nursing, 1971. Wolanin Geriatric Nursing Research Award, University of Arizona College of Nursing, 1978. Sigma Theta Tau, Beta Mu Chapter, Award for Excellence in Nursing Education, 1980. Alumni of the Year Award, University of Kansas School of Nursing, 1981. Distinguished Alumni Award, Yale University School of Nursing, 1981. Nurse Scientist of the Year Award, American Nurses' Association, 1985. Elizabeth McWilliams Miller Award for Excellence in Research, Sigma Theta Tau International, 1987. Doctor of Science Degree, University of Maryland, 1988. Doctor of Science Degree, Medical College of Ohio, 1988. Doctor of Science Degree, Marquette University, 1990. Alumni Achievement Award, University of Arizona, 1990. Distinguished Service Citation, University of Kansas, 1992. Doctor of Science Degree, University of Nebraska, 1992. Doctor of Science Degree, Mount Sinai Medical Center, 1993. Health Leader of the Year Award, PHS, 1993.

March 1, 1994

AIDS BUDGET

Mr. SMITH. Dr. Varmus, I notice that virtually every Institute tells us what they are doing that relates to HIV. How do we know how much money we are spending on HIV?

Dr. VARMUS. For some years the budget has been broken out and each and every Institute lists its efforts, AIDS and non-AIDS. In the current budget, we have a single line item in the Office of AIDS Research that is further broken down according to Institute.

Mr. SMITH. Is it possible to really know? I mean, you break it out, but as I said in the case of blood, you are doing some research and you don't know—it has some effect and you may not know it. How do you know how much we are spending?

Dr. VARMUS. There are two components to your question. One is, of course, I trust my Institutes' Directors when they tell me that this money is AIDS-related. But you are raising a very interesting and more theoretical point. There is research being done that is not labeled AIDS research but that will have a major impact on the AIDS epidemic.

We see this now because we can look in retrospect and see that many things that are extremely interesting and important such as in finding new drugs for AIDS, the use of antisense technologies, gene therapy and many other approaches, were not labeled as AIDS research five years ago.

Conversely, many of the things that are labeled AIDS research and clearly are relevant to AIDS will have major ramifications in other areas of science such as the study of the lymphoid system, a target for the AIDS virus. We know that studies of the lymphoid system that are being carried out in response to the AIDS epidemic with money designated for AIDS research are having a dramatic impact on our treatment of many diseases including approaches to the treatment of autoimmune diseases, for example.

Mr. SMITH. Also, Doctor, at this point in the record could you put more in about the reduction in the rate of maternal transmission of HIV. Could you tell us a little more about that?

EFFECT OF AZT ON MATERNAL-INFANT TRANSMISSION

Dr. FAUCI. In the United States, the percentage of transmission between an HIV-infected mother, of transmitting that either during pregnancy or at the time of delivery, to an infant is approximately 25 percent. We conducted a study that was terminated because the results were so striking among the women treated with AZT, one of the drugs that blocks the ability of the AIDS virus to replicate or divide and propagate itself. We gave either the drug to the women or a placebo, by placebo we mean gave something that didn't contain the drug, starting from the 14th week of pregnancy, but starting no later than the 34th week of pregnancy. During labor and delivery we gave the drug and we gave the drug to the infant for the first six weeks of life and then stopped.

What happened was that out of the 53 infants that were born HIV-infected, 13 were in the AZT-treated group and 40 were in the placebo group. The estimated rate of transmission in the AZT-treated group was 8.3 percent, whereas the rate of transmission in the placebo group was 25.5 percent. The results were so significant that the Data and Safety Monitoring Board terminated the study. The reason this is important, and this is a very important point, is that the drugs that we have currently available, such as AZT, have a transient effect.

You can have a benefit for someone who is already infected and make that person be disease free or live longer for a year or so, but not much longer. So the effect of the drug is limited because of the virus' ability to mutate away from the effect of the drug.

If you ask a drug to do what you want it to do for a relatively brief period of time, as in pregnancy and delivery, we now know that that is highly effective. Now, the implications for that worldwide are extraordinary. For example, there are millions of babies worldwide who are HIV-infected and born of HIV-infected mothers. In this country alone we can prevent up to 1,200 HIV infections among babies born of HIV-infected mothers because we have about 7,000 births from HIV-infected mothers.

The public health implications of this are extraordinary. If you assess the potential for health care cost saving, that is also impressive because it is estimated that it costs about $100,000 to take care of an HIV-infected baby through the time of the baby's illness. If you multiply that by the 1,000 to 1,200 babies that you can save, you are talking about potentially over $100 million a year savings. Thus, this is quite an important finding.

Mr. SMITH. Are you comfortable with the size of that sample?

Dr. FAUCI. The statisticians tell us that the size of the sample was appropriate.

Dr. VARMUS. You asked earlier about dissemination of this information, and in this case we have acted very promptly in coordination with the Public Health Service to develop a task force, in which NIH has taken the lead, to be sure that all practitioners know about this study and that the pregnant women who are out there and HIV-infected are actually brought in for treatment.

Mr. SMITH. What are the side effects?

Dr. FAUCI. The side effects on the women who were well were negligible. The side effects on the baby was a very transient anemia, low red blood cells, which very soon after the six-week treatment in the baby reverted back to normal in the babies. What we do not know is what the long-term effects on the babies will be. The short-term effects such as congenital abnormalities or teratogenic effects, or effects that have to do with the developmental process of the fetus have been essentially no different than the control group.

Built into the study is a long-term follow-up so that we will be following these babies for years to make sure that there are no long-term effects. The good news so far is that many of the babies have been followed for up to 18 months and there are no indications that there are any developmental abnormalities, and we know that most of the developmental abnormalities that we see will begin to manifest themselves at 18 months to two years. We are not 100 percent sure, but it is starting to look good.

Mr. SMITH. What about vaccines for malaria? Is there any progress being made on that?

MALARIAL VACCINES

Dr. FAUCI. One of the problems with vaccinating an individual against a microorganism that has a very complex life cycle within the host, the way malaria does, is that the ability to develop an appropriate immune response against all the different phases of that malaria parasite in the body had proven extremely problematic. However, there has been substantial effort over many years, and some interesting data from Central and South America regarding trials in individuals with malaria. I think it is too early to make any statement about that, it is using recombitant DNA technology to develop highly purified components of various stages of the malaria cycle.

Our Institute, on a national and international scale in collaboration with other agencies has a considerable effort in malaria research. I would absolutely not say it is hopeless. It is a very difficult problem, but we would hope that we are making progress and I believe that we are.

Mr. SMITH. I will get some free medical advice. I had recurrent malaria for a number of years, but I haven't had it recently. Does that mean I will never get it again?

Dr. FAUCI. In biology, Mr. Chairman, we never say never. If you have not had a relapse for a considerable period of time and you were adequately treated, it is highly unlikely that you will have a relapse now.

Mr. SMITH. Do you become immune to it?

Dr. FAUCI. Certainly, immunity plays a very important role in malaria. In countries where malaria is endemic, a substantial percentage of the population become immune after multiple exposures. You were probably exposed once but developed a not uncommon phenomenon of having one or two relapses before your immune system suppressed the parasite.

Mr. SMITH. I have probably had two dozen.

Dr. FAUCI. This was many years ago, I would imagine?

Mr. SMITH. The relationship of sickle cell anemia to malaria—— What can you tell us about that?

RELATIONSHIP OF MALARIA AND SICKLE CELL ANEMIA

Dr. FAUCI. The target of the malaria that causes much, but not all of the damage, is the red blood cell. This is the cell that manifests the genetic defect of sickle cell anemia. Apparently, if you have the genetic defect of sickle cell anemia, there is an interesting almost paradoxical protection against malaria. The same way if you have a particular blood type, you are either more or less susceptible because of the expression of a protein or receptor of that blood type.

There are things that we learn about the micro environment of a cell that would make it more susceptible or less susceptible to malaria. It so happens that in individuals who have sickle cell disease or trait, their ability to protect themselves from malaria is not necessarily an immune system response but a difference in susceptibility to malaria. We learn about both diseases by studying those differences.

Mr. SMITH. Over the thousands of years, though, they lived in the area where there was malaria, they had a better chance of survival. But then you transfer them to an area that doesn't have malaria and it is a hindrance.

Dr. FAUCI. Yes.

Mr. SMITH. Mr. Porter.

Mr. PORTER. Thank you, Mr. Chairman. Dr. Fauci, you are a former Director of the Office of AIDS Research, and I am sure you are aware of my concern about the consolidated AIDS line item and what I consider to be an abdication of this committee's appropriating responsibility should we adopt the administration's request.

In addition to the concerns I mentioned yesterday, I am concerned that the new system will adversely impact the Institute's ability to plan their budgets as they await possible reallocation of funds from OAR.

What are the implications of the President's request in your professional opinion, both positive and negative?

OFFICE OF AIDS RESEARCH

Dr. FAUCI. The process of planning both within and by using outside consultants is something that we have done all along, but the legislation and the law codified that and built up the Office of AIDS Research to make it better equipped to participate as a coordinating office in that process. I am very pleased with that concept of putting planning in a much more formal and codified way into the process of how we think about AIDS and AIDS research.

Obviously, as Dr. Varmus and others said the other day, there is nothing like a good bench discovery to take care of a disease and you can plan forever and not get it, but planning and knowing what you are doing is very helpful. We thus far have been very pleased with the process that has occurred.

With regard to the execution of the distribution of monies from the Congress to an Office and from an Office to an Institute, at this point in time as an Institute director who has more than 50 percent of my budget in AIDS, that is about $578 million, this is a paradigm that is untested: the mechanics of the process are new. So to be perfectly honest, I would have to say I have some concern, but I am very pleased with the spirit of cooperation and collaboration that Doctors Varmus and Paul have shown in shepherding and looking over this process of putting the plan together and wedding a budget to a plan.

I can't say what will happen with the logistics of it, but we will put our best effort into making it work.

Mr. PORTER. Would it be fair—and maybe this is a question for Dr. Varmus or both of you—would it be fair to say you already have made the allocation in an informal sense based on a percentage of the number? In other words, do you know about where the funds would go?

HIV RESEARCH PLAN

Dr. FAUCI. For FY 1995, we prepared a preliminary budget and then we enacted the provisions of the law prior to my stepping down as Director of the Office of AIDS research We used the existing HIV research plan that we had developed and we put together a comprehensive plan according to the outline that Dr. Varmus mentioned to you yesterday. We essentially filled in where the budget that we had developed somewhat separate from that plan for FY 1995 would fit.

So for FY 1995, the answer to your question is, yes, we have a very good idea of where the money would be going.

Mr. PORTER. Could we see that, please?

Dr. FAUCI. Yes, we could get that to you. For FY 1996, we are now in the process of putting together the preliminary budget and linking that budget to the plan.

Mr. PORTER. So, we can conclude that shortly after the appropriations process is completed and you have an appropriation for 1995, that you know exactly how that is going to be allocated and no further work is needed.

Dr. VARMUS. Mr. Porter, you have that document.

Mr. PORTER. I already have it?

Dr. VARMUS. Yes.

Dr. FAUCI. For FY 1995, that is correct.

Mr. PORTER. Let me have you talk about cost savings from research. The NIH savings book lists six entries from NIAID. Together these six improvements directly resulting from your Institute's research will save the country about a billion dollars annually in health care costs. I wonder if you would just discuss this briefly.

COST SAVINGS REALIZED BY BIOMEDICAL RESEARCH

Dr. FAUCI. Very briefly, Mr. Porter, there are a number of areas that come out pretty clearly as cost savings. One area that I had mentioned in my presentation to this Committee last year, and was conducted in collaboration with the Child Health Institute, was the development of a Hemophilus influenza type B vaccine, that is working extremely well in the community of children.

We made an initial investment of $20 million in that research, and we estimate that between $300 million and $400 million per year will be saved in health care costs.

Chicken pox varicella-zoster virus vaccine, if fully utilized in children with leukemia and lymphoma, could save $10 million a year. An improved hepatitis B virus vaccine would also promise substantial savings, over $100 million annually. Congenital herpes virus infection vaccines are already showing cost savings, and the public health implications are significant considering the number of infants born of women who have either latent or activated herpes virus infection.

Organ transplantation with immunosuppression and better typing has saved between $40 and $60 million. Finally, is the area that I just mentioned in AIDS. There we have not only in the specific case of maternal fetal transmission, but also another area that is not really very well appreciated and that is antiretroviral therapy, the treatment and prophylaxis of the opportunistic infections that HIV individuals get when they have advanced disease. If I were to pick out the single most important advance, not only in the health of HIV-infected individuals but in cost savings, I would say it is how we are treating and prophylacting or preventing these opportunistic diseases such as Pneumocystis carinii pneumonia.

Mr. PORTER. I have a couple of more questions. Dr. Varmus, has the NIH taken a position on the legislation that has been offered in the Senate to provide a 1 percent tax on health insurance premiums in order to create a funding stream for biomedical research?

Dr. VARMUS. As you know, Mr. Porter, we are part of the administration and we support their plan for health care reform. We will take a position publicly in support of the Administration's reform plan.

Mr. PORTER. This is not in opposition of their plan.

Dr. VARMUS. We take a more favorable view of more funding for NIH in general, but we are concerned about having health care reform and we will abide by their decision whether to advocate for additional costs associated with insurance premiums.

Mr. PORTER. Dr. Fauci, I have one more question. I want to thank you for the work that you are doing on chronic fatigue syndrome. You explained very well the progress that you are making and the priority which you are placing on it and I am very encouraged by that.

Finally, you have an award rate for 1994 of 46 percent for AIDS and 20 percent for non–AIDS grants. Forty-six percent is above the 40 percent level that Dr. Varmus told us we ought to be shooting for, but the 20 percent rate for non–AIDS is very, very low.

For 1995, the gap would close somewhat to 38 percent and 27 percent, respectively. No other institutes have anywhere near this disparity. Why does NIAID have this disparity and is it appropriate in your professional opinion?

AWARD RATE

Dr. FAUCI. I could answer the second part of the question succinctly and go back to the explanation for the first part. No, I do not think it is appropriate, but I would not want that at all to indicate that I don't think that the money in AIDS is very well spent. I do believe that it is. When you talk about dichotomies and discrepancies, that is a problem. You might recall that this Committee last year spent considerable time pointing out that we had a major dichotomy last year in the budget where we had targeted areas, one of which was AIDS and HIV, which for my Institute was an 18.1 percent increase from 1993 to 1994.

Simultaneous with that, we had a couple of other targeted or investment areas such as vaccines and tuberculosis. If you extract the targeted areas and look at the other components of the Institute, in fact, it was reduced 7.5 percent from 1993 to 1994. When the Senate and the House came back and tried to fix that, because they wanted to bring the other Institutes to at least a 5 or 5.2 percent overall increase, money was put back into the other Institutes and nontargeted areas, but NIAID, because our overall increase was 8.3 percent it was felt, understandably for you all but not good for us, that since we had a total 8.3 percent increase that no additional money in non–AIDS should be put back into the budget.

So what we had was an extraordinary gap which resulted in more than 40 percent because we have an 18 percent increase in AIDS and 20 percent in non–AIDS which causes, as you might imagine, some consternation in the communities.

This year the gap is certainly much, much less but that is the explanation for the phenomenon that you pointed out.

Mr. PORTER. Thank you, Dr. Fauci. I will save my questions for Dr. Leshner and Dr. Hinshaw for round two.

Mr. HOYER [presiding]. I am going to ask a couple of questions. Leadership in large sense is just waiting in the room long enough and you just take over; right?

ANTIBIOTIC RESISTANCE

Dr. Fauci, let me ask you something unrelated to the budget per se, but I am interested in it. I saw a television program about the increasing phenomenon of viral diseases becoming immune to some of the super drugs that we have used over the last 40 years. Is that within your bailiwick?

Dr. FAUCI. Yes.

Mr. HOYER. Tell me about that.

Dr. FAUCI. Mr. Hoyer, it isn't viral diseases. It is microbes in general. We have very few therapies against viruses in general. They are referring to antibiotic resistance and that is a phenomenon that has been around for a long time, but is exacerbated by the use sometimes, and often inappropriately, of antibiotics against a particular microbe.

All microbes have an ability to replicate reasonably rapidly. With replication comes a natural mutation so that it doesn't all replicate the same. Interestingly, among microbes—not to get back to HIV—but HIV because of the mechanism that it uses has an extraordinary ability to mutate. But putting that aside for a minute, let me get back to your direct question.

There are certain things that pressure microbes to use their ability to mutate for the benefit of their own survival so that if the immune system makes a response against a microbe that shows itself in this way, the microbe by selection of its own propensity to make itself survive will change a little to escape the immune system. If you throw a drug into someone and treat them with a drug, though that drug kills most of those microorganisms in its mutational tendency to survive, it will change to avoid the drug.

So what happens if you have the combination the body's immune response against the microbe together with what is very often inappropriate use of antibiotics? Then you have a phenomenon where there are microbes that would otherwise be handled very well either by your body's immune system or by an antibiotic but which all of a sudden are very, very resistant and that is when you get in trouble. That is when people in the hospital with something as common and easy to treat as a urinary tract infection find out they have a microbe that the antibiotics are very ineffective against.

We see that with things like bacteria in urinary tract infection and a very cogent example of that is multiple drug resistant tuberculosis, which because people who get tuberculosis, particularly in the HIV epidemic, generally don't take the full course of their therapy. So that the microbe starts to change a bit to avoid the therapy and then you pull the therapy away and the resistant microbe just flourishes and that is a very serious problem. What you happened to see on TV did reflect a true problem.

Mr. HOYER. Presumably, therefore it is quite a focus of your Institute.

Dr. FAUCI. Yes, indeed.

Mr. HOYER. I have five minutes. I might as well go vote. I presume the Chairman will be back shortly.

[Recess.]

Mr. STOKES. Should I proceed, Mr. Chairman? Thank you, Mr. Chairman.

Dr. Fauci, why don't I start with you and we will try to work over to the other two directors.

Dr. Fauci, over the past several years you have provided the Committee with periodic updates on the Institute's Introduction to Biomedical Research Program which is designed to provide students from underrepresented minority groups an orientation on career opportunities in biomedical research. I understand you have recently done an evaluation of this program. Would you share that with us?

INTRODUCTION TO BIOMEDICAL RESEARCH PROGRAM

Dr. FAUCI. Yes, Mr. Stokes, I would be very happy to share that with you because it was very pleasant news and surprisingly pleasant. I didn't think it was going to be as good as it was. We went back and looked at long-term follow-up. The program has been going on for many years as I report to you yearly. We went back and looked at the results of the first four years of the program in which we were able to follow the students and we followed 188 of them from those first four years.

One-hundred seventeen of them graduated from medical school or are currently enrolled in medical school. Seven of them have received their Ph.D.'s and 40 of them are now being supported on grants.

These results give us all the more energy and enthusiasm about continuing and accelerating that program. So I am very pleased to report that to you this year, Mr. Stokes.

Mr. STOKES. Thank you very much. As Director of one of the Institutes at NIH, tell me how you would respond to this statement: The minority health crisis continues while we continue to witness an unprecedented explosion of scientific knowledge, a phenomenal capacity to treat and cure disease. While medical and technological breakthroughs are affording Americans a longer life expectancy, we still find the minority health crisis continuing. Would that be an accurate statement?

MINORITY HEALTH CRISIS

Dr. FAUCI. I think it is accurate, Mr. Stokes, and I think what it reflects is a very complex problem that we have had a sobering full dose of, particularly in our areas of research, but not exclusively with us. It impacts on a lot of other Institutes, but we have had a good dose of it in our HIV, and our inner city sexually transmitted disease network, tuberculosis work.

The system now is such that minorities find themselves unable to benefit from advances in biomedical research, and even unable to participate in clinical research trials. The ability of minorities to get themselves into those trials is beyond their control and impedes these individuals from obtaining standard health care.

And for that reason, as I have discussed with you at these hearings and privately over the last several years, we have tried to integrate that concept and to try to do something about it with our clinical trials process, such as our AIDS clinical trial group, our community programs, and in fact each year, minority participation improves.

I was pleased last year to report to you that we are inching up very nicely so that the number of individuals who are in an NIH-sponsored program that gives state-of-the-art availability for things like clinical trials is rapidly approaching the relative proportion of minorities who are actually afflicted with the disease. So your statement perplexes me and saddens me because it is true, and we have a long way to go before we can equalize that.

One of the ways we as a research institution can do something about that is to try and make our research findings more widely disseminated, which we try to do, and ensure that our clinical trials process is sensitive to the needs of minorities. I don't deny that we have a way to go.

DRUG RESISTANT TUBERCULOSIS

Mr. STOKES. I appreciate your response to that question.

On another issue, last year, we talked about tuberculosis not only being recurrent but also being drug resistant in some respects. What is the current situation?

Dr. FAUCI. The current situation is that it is still bad. One little bit of light at the end of the tunnel is that recently in New York City, because of an intensification of the direct observation of therapy program and what I would call a full court press by the health officials in New York City, the TB incidence has now started to plateau a bit and come down.

I say that with some trepidation because if we could transplant ourselves back 30 years I could say, well, now it is not a problem anymore.

It is still a serious problem, and our Institute and a number of other institutes at NIH have responded with a TB research agenda that will get us back into the modern age, not only in the basic biology and pathogenesis of tuberculosis, but also in better drugs, better vaccines and better diagnostics.

We have intensified our efforts and we will continue to do that. It also shows that if you put a public health effort into it, you can also have an impact. It needs to be a wedding of the both of them, the basic science and the public health execution of programs.

DRUG ABUSE IN THE U.S.

Mr. STOKES. Thank you very much. Let me move to Dr. Leshner, the Director of the National Institute on Drug Abuse. Dr. Leshner, in terms of the drug problem, would you agree that the United States probably stands alone as being the Nation which has the greatest drug addiction, drug abuse, and drug dependence. No other Nation in the world has this record.

Mr. LESHNER. I believe that we do have the highest rates of drug addiction.

Mr. STOKES. Do we know why?

Mr. LESHNER. I don't, sir. We could do some further research on it and get you an answer on that.

[The information follows:]

CAUSES AND CONSEQUENCES OF DRUG ABUSE IN THE UNITED STATES

The United States is often cited as having the most serious substance abuse problem in the industrialized world. This assertion is based primarily on the availability of comprehensive data from ongoing information systems that have been operating for several decades in this country. However, the assertion has been made in the absence of comparative epidemiologic information from other countries. NIDA has recognized the importance of assisting countries throughout the world in developing drug abuse surveillance systems similar to those in the United States, yet adapted to the unique circumstances and resources of each country, and these efforts are continuing.

It is clear that we in this country have a serious problem with drug abuse and drug dependence. According to the National Household Survey on Drug Abuse, there were 11.4 million current (30-day) users of illicit drugs in 1992, and recent estimates suggest that as many as 2.5 million users could benefit from treatment. Most are addicted to cocaine, especially crack-cocaine, often in combination with other illegal drugs and alcohol.

Societal norms play an important role in drug abuse. For example, as the public attitude continues to change and drug abuse is no longer viewed as a "rite of passage", drug use in the United States is seen to be decreasing. On the other hand, the United States is an open society, and individuals are free to make their own choices about drug use. As other countries become more open, drug abuse and drug dependence can be expected to spread. Significant increases in rates of opium and intravenous heroin addiction are now being found in many countries of South and East Asia, and dire warnings are being forecast regarding heroin addiction in countries of Eastern Europe.

While much has been learned about individual vulnerability to drug abuse, and treatment and prevention strategies have been developed and applied for various types of patients and differing population groups, many of the problems that contribute to drug abuse still need to be better addressed. These include environmental, social, behavioral, and biological factors. Understanding the causes and consequences of drug abuse requires knowledge not only of the immediate and long term actions of pharmacological agents, but also of the complex cognitive and motivational processes underlying brain function, which lead to drug seeking behaviors.

Sufficient information on the factors which predispose or protect an individual from escalation to and maintenance of drug abuse currently exists to allow the development of high risk indices and profiles. Early vulnerability markers include, for example: having family members who are substance abusers; demonstrating delinquent behavior or alcohol, nicotine or illegal drug use at an early age; association with drug abusing and delinquent peers; early signs of psychopathology or difficulty in emotional regulation or impulse control; and living in an environment with high drug availability, family disruption, and/or peers and adult role models who use drugs. The early identification of children and adolescents at high risk for drug abuse makes targeted early interventions more feasible and thus may facilitate more effective drug abuse prevention.

Research has demonstrated that psychological, psychiatric, and cognitive development impairments may contribute to drug abuse, and drug abuse may exacerbate these conditions, creating a mutually reinforcing dysfunctional system. More information is needed on interrelationships between drug abuse and various psychosocial, psychiatric, societal, cognitive, developmental, biobehavioral, physical, and health consequences. Research on how risk factors covary, and on how reductions in one risk factor may affect other risk factors, might help produce strategies for addressing a number of pressing health and social problems. More research is needed on the comorbidity of drug abuse with mental disorders, alcohol abuse, physical disease, criminal involvement, accidents, sexual involvement, and environmental factors such as low economic status. Such research would focus on issues of causality, through longitudinal studies and analysis of the interdependence of deviant behaviors and comorbid conditions.

Mr. STOKES. In terms of the research that your Institute is involved in, what are the most important research initiatives underway to address this problem.

Mr. LESHNER. We are trying to take a multiple strategy approach towards drug abuse. One set of initiatives that we have is looking at the fundamental etiology, the causes, and the biological mechanisms underlying drug abuse and drug addiction. The reason that that is important is that we are badly in need of therapeutics, and we need to have new treatment modalities. To do this we need to have the fundamental understanding at which to direct those therapeutics.

However, there are several millions of drug abusers on the street, and they need treatment now. Although treatment can work, and is highly effective for many individuals, it is not effective for many other individuals. Therefore, a major NIDA effort is being directed towards improving the efficacy and the effectiveness in real life settings of treatment modalities. That involves looking at culturally appropriate outreach efforts and culturally appropriate treatment efforts.

Tied to that, we are trying to build an infrastructure for clinical research on drug addiction treatment. There are far too few people who view drug abuse as truly a public health problem. Therefore, a major focus of our efforts is to try to bring a larger proportion of the health community into research. This, of course, will have the consequence of impacting on drug abuse related to AIDS and a variety of other related issues as we bring more and more medical personnel into this arena.

Mr. STOKES. Dr. Leshner, now that the Institute has identified and genetically specified the molecular sites in the brain where major drug abuse has its initial effect, how will that information be used to advance and accelerate methologies to address drug prevention and intervention?

Mr. LESHNER. This is an example of one of those sets of basic research findings that I mentioned before, and your question is an extremely good one. We are in a situation where, having made these advances in the fundamental neuroscience of addiction, we now can begin to do what we call "rational" medication development, rather than "opportunistic" medication development.

In the past we used techniques of screening drugs, drugs that were on the shelf—hoping that one would prove effective in our various screening protocols. Now, for example, for cocaine, for which we don't have an effective medication, the knowledge of how cocaine is working in the brain reward system allows us to begin to develop medications, chemical substances, that target a particular area.

Let me give you a quick example. Cocaine works on the dopamine reuptake transporter and it blocks that. The result is that there is too much dopamine flowing in this particular part of the brain. The problem is you don't want to totally block dopamine, so what you need is a cocaine-blocking, but dopamine-sparing chemical. The knowledge that you referred to gives us an indication that we need to look for that kind of an approach.

Mr. SMITH. Mrs. Bentley.

Mrs. BENTLEY. I will pass to Mrs. Lowey.

SAFE DRINKING WATER ACT

Mrs. LOWEY. Thank you, Mr. Chairman. Dr. Fauci, your testimony refers to recent incidents in which infectious organisms have compromised the water supply in several cities; in New York and Washington, D.C. As you know, Congress is in the midst of reauthorizing the Safe Drinking Water Act under which standards are set for drinking water quality.

An issue in the reauthorization is whether public health agencies are appropriately regulating drinking water contaminants and whether some of these regulations are specifically sound.

Can you elaborate on the nature of the Institute's involvement in this issue and has the Institute played any role in providing scientific analysis to guide the reauthorization?

Dr. FAUCI. Mrs. Lowey, to my knowledge we have not been involved in those aspects of it. Our Institute, as you know, does basic and clinical research on a variety of microorganisms and the immune responses to them, but we have not been involved to my knowledge—and I am pretty sure I would know about it at this level—in any policy-making or any guidelines regarding the public health aspects of the water supply that you talk about.

Mrs. LOWEY. Should you be?

Dr. FAUCI. Well, I think the knowledge regarding the fundamental nature of the organisms, their survival and things like that, are offshoots of the kinds of research that we conduct. I am not sure whether we should as a research agency be playing a major role in anything that has to do with regulation of public health processes like you are talking about.

I hope I am not misspeaking, but my own feeling is that as a research agency, we are always available for consultation and readily do that with a number of agencies that do have regulatory mandates, but we are not intimately involved in that process.

Mrs. LOWEY. Thank you.

LYME DISEASE

As you know, because we have spoken about it, there is a good deal of controversy around the issue of whether prolonged use of home infusion therapy is an effective mode of treatment for Lyme disease. Can you discuss what the research shows in that area and are there plans for further research directed at this particular question?

Dr. FAUCI. The answer to your last question is certainly there is. As you know, we have discussed with you and your staff accelerating our effort in Lyme disease. One of the real problems with Lyme disease is that the microorganisms have the capability of persisting in tissues, such as the joints. In addition to that, there is a component of the natural history of disease that enters into a state of chronicity, mainly an individual can get acute Lyme disease today and then a month or two or three or several months down the line, they may still have some persistent symptoms.

What we don't know and what our research is directed at are two things. First, developing better diagnostics using molecular probes for the microorganisms such as polymerase chain reaction or PCR to identify in tissue the microorganism to make a correlation between the presence of the microorganism and a chronic symptom. Since that has been an inexact science because there have been indications where we couldn't find the microorganism, you have to obtain more sensitive and better diagnostics.

Secondly, we have to learn a lot more about how you can have a delayed symptom when you don't have the microorganism present. That is probably due to an aberrant immune response against certain components of the microbe that trigger off instead of just clearing the microbe and disappearing. When this occurs you have what we call the paradoxical propagation of disease by the immune response.

These are very complex issues, but that is exactly what our research is aiming at right now. The difficulty is that people in their frustration and sometimes desperation about symptomatology would get involved in treating themselves for a very, very long period of time at home. As you know, there are some rather qualified experts in this particular area who don't feel that that approach is really based on any solid scientific evidence, which even compounds more the need to do the kind of research that we are doing. It is not a trivial problem.

WOMEN'S HEALTH

Mrs. LOWEY. You also mention in your testimony that women are six times as likely to suffer from autoimmune diseases. Can you describe the Institute's research in these diseases and any special initiatives directed at women?

Dr. FAUCI. Yes, the answer is there are a number of diseases. I think lupus, systemic lupus erythematosus, is one of the most obvious of those. What our Institute is doing is that we are involved at the fundamental level of understanding how the immune system regulates itself. Most, if not all, of these autoimmune diseases are related at least in part, to what we call a dysregulation of the immune system or because the immune system responds inappropriately to some sort of endogenous stimulus, something that you are exposed to from the environment.

By fundamental research, which is a substantial proportion of our portfolio and understanding those precise mechanisms, we are going to learn a lot about why women are more prone to this. It almost certainly has to do with something about women that is different from men. The first obvious things that you think about are sex hormones. In fact, there has been a considerable amount of research, particularly in a mouse model, to look at what manipulating the sex hormones in the mouse, either making the mice more susceptible or less susceptible, would do to the onset or propagation of autoimmune disease.

We are doing that. We are doing it in coordination with the Arthritis Institute and a number of other institutes. That is a very intensive area of research.

SUBSTANCE ABUSE TREATMENT

Mrs. LOWEY. Thank you. Doctor Leshner, in my remaining time, the President has requested a significant increase in the drug treatment budget. And the proposal would target resources on hard-core drug users. Some opponents of the President's proposal claim that it is inappropriate to invest this much in substance abuse treatment, particularly in hard-core users, because we have not yet developed treatment methods that have clear records of success.

I would appreciate your response to this. And in fact, in my time on the Select Committee on Narcotics Abuse and Control, what was so frustrating to me is that there are a lot of good things going on around the country. I am familiar with Phoenix House, Day Top and others, but we didn't sort out in my judgment sufficiently what works and what doesn't work. And if you try to explain to people that it is important to continue investing in this, it seems to me that we really have to get some good evidence.

How would you respond to those who say it is a waste of money? It is not going to work anyway. The recidivism rate is too high. What are you doing it for?

Mr. LESHNER. There are a couple of ways to approach that question. Probably the best way to begin is by making the point that drug abuse, and particularly addiction, treatment can work. There is a large body of efficacy data available that says, "For people who stay in treatment, treatment can work." Let me add to that, when people do stay in treatment, it is tremendously cost-effective. That therefore ties to the President's approach in health care reform. In fact, if you look at just methadone treatment alone, it has had fantastic cost savings. Methadone treatment costs just $3,600 per year, but in reduced crime alone it appears to save as much per month. That is a fairly dramatic cost-saving phenomenon.

The biggest problem is that we don't quite know enough yet about two aspects of the treatment problem. One is that not all treatments work for all individuals. That is why we say "treatment can work," not "treatment does work". Therefore, a lot of what we need to do is treatment matching studies. There are tremendous differences in the approaches you might use for a variety of groups, and that is the most difficult part of it.

But the fact is, treatment can work and work for a large number of people, though it also does not work for a large number of people. We are in the process of constantly improving treatment and that is one of the reasons explaining the investment at NIDA of a large treatment research portfolio that looks both at the treatment efficacy issues and developing new treatments and improving existing treatments.

Mrs. LOWEY. My time is coming to an end, but I would be most appreciative of any information that you have to submit for the record on any of these treatment matching statistics. We have been talking about this for a long time. And I think if we are going to be good advocates for you and to get continued increase in these budgets, we will have to show someone that it works.

Mr. LESHNER. We do have efficacy data and I will be happy to submit that for the record.

[The information follows:]

MATCHING PATIENTS TO APPROPRIATE TREATMENTS

The degree of effectiveness of a given episode of treatment depends upon individual factors and upon program factors. Individual factors include the presence of underlying co-morbid physical and psychiatric conditions; the client's goals, expectations, and motivation to change; the client's level of social adjustment; and the presence of other legal, family, or social problems that, while they may or may not be related to the drug problem, will if not resolved predispose the client to relapse. Treatment of coexisting psychiatric problems, for example, has been shown to improve treatment outcomes and reduce relapse. Program factors include the training, experience, and expertise of the treatment staff; the clinical treatment model employed; the ability to attract drug abusers to treatment; the development and implementation of treatment plans and services that are appropriate to the needs of the client; and the ability to retain clients in treatment and to engage them in long-term aftercare and relapse prevention programs.

Matching patients to the appropriate treatments results in increased treatment engagement, retention, and compliance. For particular subgroups of patients there is reason to believe that particular types of therapies may be more useful than others. For example:

Kadden and colleagues at the University of Connecticut have demonstrated that a structured, behavioral therapy may be more effective for substance abusers with sociopathic characteristics than an interactionally focused therapy. Woody and colleagues at the University of Pennsylvania have shown that in subgroups of patients with antisocial personality disorder who have an additional diagnosis of depression, cognitive-behavioral and supportive-expressive psychotherapy is of benefit. However, antisocial personality disorder alone appears to be a negative indicator for response to psychotherapy.

There is evidence from researchers at the University of Pennsylvania that addition of psychotherapy to drug abuse counseling may be necessary for certain subgroups of addicts. Providing psychotherapy to low psychiatric severity methadone-maintained opiate addicts who are already receiving drug abuse counseling does not appear to yield any further benefit. However, in methadone-maintained opiate addicts with high levels of psychiatric severity, psychotherapy in addition to drug abuse counseling is significantly more effective than drug counseling alone.

Rounsaville and Carroll at Yale have found that severity of cocaine abuse interacts with therapy received, such that high severity patients do better with Relapse Prevention than Clinical Management and low severity patients do better with Clinical Management than Relapse Prevention.

The confrontational approach often utilized by counselors in groups or individual settings to break down male addicts' denial is often counterproductive with female addicts, serving only to further decrease the already minimal self-esteem experienced by most addicted women. While male addicts derive the most benefits from groups that are mixed, female addicts often respond better to group situations without men.

While we know a great deal about the factors that impact on treatment, a better understanding is needed on ways to encourage and direct patients to the therapy that will be the most effective for that individual. NIDA has established the Behavioral Therapy Development Program to parallel NIDA's Medications Development Program. This program builds on basic behavioral and clinical studies to: 1) develop, refine, and pilot test new behavioral treatment strategies and 2) conduct clinical trials to test the efficacy of promising behavioral therapies. A major focus of these clinical trials will be to improve the matching of clients to treatment. The transferability to the community of therapies proven to be efficacious in a replicated clinical trial will be assessed through studies in community settings. Ultimately, therapies found to be valuable in the community setting will be disseminated to clinicians.

Mr. SMITH. Mrs. Bentley.

Mrs. BENTLEY. Thank you, Mr. Chairman. Dr. Leshner, it is my understanding that NIDA has been participating in research that involves the use of fenfluramine and phentermine, two medications that have been used for weight loss control. Apparently, when the two substances are combined, they can be used to control the craving for crack cocaine. Can you bring us up to date on that research?

Mr. LESHNER. While I don't know a great deal about fenfluramine, I can tell you that it is part of a broader medication development program that we support where we are looking at a variety of medications and screening them for their potential in drug abuse. The combination that you mentioned is one of the medications that is being considered and I can get you some more information for the record.

[The information follows:]

FENFLURAMINE/PHENTERMINE FOR TREATMENT OF COCAINE ADDICTION

In February of 1993, Dr. Pietr Hitzig, a clinician practicing in Maryland, published an article in the Maryland Medical Journal on his use of a combined dopamine and serotonin agonists approach to alcoholism and other addictive behaviors. Reporting on the first 11 patients treated by him for alcoholism with a combination of Fenfluramine/Phentermine (FEN/PHEN), Dr. Hitzig observed that all patients responded well to the medications and stopped drinking for an extended period of time. Following the publication of the paper, Dr. Hitzig contacted a number of scientists who work in the area of drug abuse research, including those at the NIDA intramural program at the Addiction Research Center (ARC) in Baltimore. ARC scientists reviewed his findings, and felt that the preclinical research literature supported the testing of these agents as substitution-type medications.

When Dr. Hitzig began treating cocaine addicts, he invited ARC scientists to his office to observe his treatment. After following the first 6 cocaine addicts treated by Dr. Hitzig with FEN/PHEN through four weeks of treatment, ARC scientists were impressed with the apparent ability of these medications to suppress cocaine-craving and to help these patients abstain from the use of cocaine. A report of this case series will soon be published.

In light of these experiences, ARC scientists have decided to organize a double-blind placebo controlled study of the efficacy of FEN/PHEN as a treatment for alcoholism and cocaine addiction. This protocol is in the final stages of Institutional Review Board approval. ARC scientists are also preparing a protocol to study FEN/PEHN for treatment of cocaine addiction, which will soon be submitted to the Institutional Review Board for review.

A study of the effect of FEN/PHEN in "normal" humans is already under way in collaboration with Dr. deWit (University of Chicago) and Dr. Johanson (ARC). The ARC Clinical Psychopharmacology Section also has several studies under way in animals, including in vivo microdialysis studies and studies in a mouse model of cocaine-reinforcement. In collaboration with scientists at NIDDK, NIDA is examiing the effect of FEN/PHEN on cocaine self-administration in rhesus monkeys. NIDA's Medications Development Division is also coordinating several animal toxicology studies of FEN/PHEN and its interaction with cocaine.

Mrs. BENTLEY. Do you know whether or not Johns Hopkins is involved in this?

Mr. LESHNER. I do not.

Mrs. BENTLEY. Does the name, Dr. Pietr Hitzig, mean anything to you?

Mr. LESHNER. Yes, ma'am. He is working with NIDA staff.

Mrs. BENTLEY. He has been experimenting with these for a long time. I have met with him on a couple of occasions and he said that he had been studying these primarily for weight loss control, and in working with them more, said that there may be an application for treatment of a variety of disorders that may revolutionize psychiatric treatment. The most exciting aspect is its amazing potential to control craving disorders for alcohol, cocaine, crack cocaine. In as little as two hours.

This effect seems to last as long as the patient continues to take the medication. Apparently, these medications are available to the patients at a prescription cost as low as a dollar and a half a day. The side effects are minimal. The patients are not only free from their addiction, but their frequently associated symptoms such as depression, rage, and paranoia also abate.

Although 190 alcoholics have responded with a 85 percent success rate, and 72 percent of cocaine addicts are now leading functional lives, this unprecedented response does not meet the criteria to satisfy the medical community. To complete his clinical research, a double blind study is necessary. There is such an alcoholic study ready to be implemented. This program will be broad-based and involve patients from the VA hospital, researchers at NIDA and Veterans Administration and Dr. Hitzig. Further cocaine double blind studies will also be implemented.

I met with this man, and he seems to be an honorable person. I think it really is important that some efforts be made to explore and look into this combination of drugs and whether it is worthwhile.

Mr. LESHNER. It is my understanding from my colleagues that NIDA researchers at the Addiction Research Center are collaborating in part on this project, and they are doing a phase one toxicity study.

Mrs. BENTLEY. Phase one toxicity study— meaning what?

Mr. LESHNER. They are looking at whether it can be administered in humans and looking at the initial indications in humans. Evidently, most of the data so far are primarily anecdotal from a single physician.

Mrs. BENTLEY. Is any of this being conducted in connection with the Addiction Research Center?

Mr. LESHNER. Yes, ma'am. The Addiction Research Center is involved.

Mrs. BENTLEY. What level of programs are planned for fiscal year 1995 and how does it compare to 1994?

Mr. LESHNER. On that project? I don't know.

Mrs. BENTLEY. Could we find out?

Mr. LESHNER. Yes, of course.

[The information follows:]

This year, in fiscal year 1994, ARC will spend approximately $100,000 for research on fenfluramine/phentermine for treatment of substance abuse, and this amount is expected to more than double in fiscal year 1995.

Mrs. BENTLEY. Last year when I asked one of the Institute directors about the Gulf War syndrome, I don't recall receiving too much in the way of hard information. What have we learned about this ailment in the last year?

Mr. LESHNER. I don't know about it. I don't know whether it is a drug addiction problem.

Dr. VARMUS. There is going to be a conference held on this topic partly sponsored by the NIH in late April. We had been approached about sponsoring a consensus conference. We are expressing the concerns of those who are interested in the syndrome and support a public meeting on this topic.

CHRONIC FATIGUE SYNDROME

Mrs. BENTLEY. I know that your Institute has conducted a good bit of research on chronic fatigue syndrome. Can you tell me what exactly—what is the relationship between chronic fatigue syndrome and the Epstein-Barr virus and how will the Epstein-Barr symptoms compare with CFS?

Dr. FAUCI. The chronic fatigue syndrome originally was referred to as chronic EBV infection because the initial investigations indicated that there was what we call serologic evidence or immune response evidence that was either recent or persistent infection with Epstein-Barr virus.

Subsequent to the more intensive scientific and basic scientific and clinical investigation of the chronic fatigue syndrome, it became apparent that this was not the case and such that the etiologic agent or agents that lead to a syndrome which we call chronic fatigue syndrome and that there is no good solid evidence that it is, in fact, chronic EBV. There have been a number of multicenter studies including a component of intramural research that have been contributing to that. So it is still a perplexing problem as to what the etiology is. People no longer call chronic fatigue syndrome chronic EBV infection.

Mrs. BENTLEY. Where is the Institute's research in regard to the Epstein-Barr virus?

Dr. FAUCI. The Institute is involved in the research involving EBV as one of the many virus microbes that we study. The Institute is also involved in another group of studies involving chronic fatigue syndrome, but the direct relationship between the two has defied scientific documentation.

Mr. HOYER. I am up. Thank you. Dr. Fauci, let me ask you a couple more questions. You mentioned in your testimony that STD infection seems to increase one's chances of contracting the HIV virus.

Can you explain why this seems to be the case?

RELATIONSHIP OF STDS AND CONTRACTION OF HIV

Dr. FAUCI. Yes, good natural history in epidemiology studies have indicated that if an individual has an ulcerative genital disease, namely a sexually transmitted disease, that causes an erosion of the skin of the mucous membrane of the genital tract, that there is up to a five times greater chance of that individual either getting infected from a partner who has the virus or actually transmitting it because more virus is shed when you have ulcerative diseases.

One of the strategies we are pursuing and which has brought general STD research into HIV research, and has brought topical microbicides into all of them, is the fact that if you can reduce sexually transmitted diseases and treat them quickly and effectively, it is very likely that you would be able to decrease the transmissibility of HIV.

In fact we have some clinical studies that are on going both out of this country and in this country looking at the relationship between the prompt treatment of STDs and the ability to block transmission of HIV. This is very important research.

NIAID AND CDC COLLABORATION

Mr. HOYER. That being the case, and I would like Dr. Varmus' answer about the administration's point of view, wouldn't it argue for an increased effort in CDC on STDs?

Dr. FAUCI. We work closely with the CDC on STD. We do different components of what I consider a complementary effort, namely, they are involved predominantly in the phenomenon of STD spread, the surveillance, and the natural history.

We are involved in that, but with much more of a biological component. Also, both of us are involved to some degree in behavioral research.

I think that you cannot have one without the other, and for this reason, a considerable amount of our STD effort is conducted in collegial collaboration and cooperation with the CDC.

In fact, the former head of our sexually transmitted disease branch of our division of microbiology and infectious diseases now heads up the STD program at the CDC. It has strengthened an already existing program.

The answer to your question, should there be more in the CDC, this is an unusual situation.

Mr. HOYER. Let me rephrase the question.

Dr. FAUCI. Okay.

Mr. HOYER. If more resources were available for CDC, STD programs, wouldn't that help slow the spread of HIV infection?

Dr. FAUCI. The answer is that the opportunities for the CDC, as well as the NIH I might add, to intervene in these very important areas are quite directly related to the transmission of HIV, and the scientific and public health opportunities, in my opinion, are greater than the resources available.

Mr. HOYER. Thank you.

Dr. Leshner, as you know, one of the reasons we have been running in and out of this room is because we have a crime bill on the floor. Obviously everybody is interested in punishment. On the other hand, I also believe that substance abusers do not, because they are substance abusers, fall into a criminal category. They fall into a category that obviously they are involved in criminal behavior, but they are hooked and many really want treatment.

We are including a lot of money, as you know, for rehabilitation in this bill, which I support. The public needs to have a far higher level of confidence than they do that whatever monies are spent on rehabilitation will be cost-effective.

Now, you mentioned there was some success, treatment can work if people want treatment. Now, that may not be a direct quote, but your point was, if the alcoholic using it admits he is an alcoholic, that is the first step. Can you tell us briefly whether we are making progress?

Mr. LESHNER. The simple answer is yes. Let me start by agreeing with your position that people who are addicted to drugs are disabled and are suffering from a disease. In my view, a brain disease. It therefore requires a complex treatment modality. It also requires by nature of the effects of drugs on people, a very complex set of treatment approaches in order to bring them back to full productivity in society; and therefore it is a multifaceted strategy.

First of all, as to criminality, I cited a statistic before, but I would like to cite it again, and that is that treatment is cost effective. Methadone costs $3,600 a year as a treatment approach. Studies show that it saves $3,300 per month, the amount required to incarcerate a person in jail. And it saves by decreasing the criminality of people who have been in successful treatment. It saves $40,000 to $50,000 a year per person in overall societal costs, including reduced crime. So treatment when it works, is highly cost effective.

It also is the case that we are constantly improving our treatments. I too am sympathetic to the concern that people have that engaging people in treatment is very difficult and that it is a complex task. However, if you look at the efficacy rates over time, they are constantly increasing, and I would like to believe the research is playing a major part in that.

We are looking at multiple modalities. NIDA in the last few years has begun a major behaviorally oriented treatment research program trying to foster the development of wholly new treatment approaches that will look at particular populations at risk; but there are data about efficacy, about engagement and about outreach that show that existing treatments are effective.

Mr. HOYER. I presume that there is a very close working relationship between your Institute and the National Institute on Alcohol Abuse and Alcoholism.

Mr. LESHNER. Certainly.

Mr. HOYER. Thank you, Dr. Leshner, I'll submit my additional questions to you for the record because the time is limited.

Dr. Hinshaw, I have been told that this may be your last visit with us; is that correct?

Dr. HINSHAW. That is correct.

Mr. HOYER. That is our loss. I want to say how proud we are of the work that you have been doing. NINR does very important work and we appreciate your leadership. Let me ask you some questions if I can.

NINR FTE REDUCTION

I am very concerned about this reduction we have made in the federal workforce. Dr. Varmus raised an issue which I really hadn't come to grips with yesterday that my staff and the Federal Service Task Force are going to be working on in terms of the impact of workforce reductions on NIH's scientific personnel. They aren't your average federal midlevel administrators.

As the smallest Institute, can you tell me what impact your portion of this 252,000 cut will have on your Institute?

Dr. HINSHAW. Well, I think the biggest difficulty is the long-term ramifications. We are all aware of the need to cut back. I think we are all in support of that.

It is when you are among the smallest groups you know there is a particular critical mass that must exist. Even though we are a small Institute, you must conduct all of the activities and assume all the responsibilities that any other NIH Institute assumes. Because of that, we have a certain number of activities and staff that have to be maintained.

There really is probably a critical mass that you can't go beyond, and that is where we may begin to hit problems. The NINR is decreasing only about one person a year over the next several years, but that will take us close to 45 people by the time this plays out. That could be below the critical mass level.

HEALTH CARE REFORM

Mr. HOYER. Last question to you, Doctor. The change in health care driven both by the marketplace and, we hope by the passage of health reform will make the nursing profession even more central in the field of primary care.

Your Institute is a key part of the future of nursing in this country in my opinion, and I wonder if you could share with the Committee how research supported by NINR fills gaps not addressed by the research of other Institutes.

Dr. HINSHAW. Well, when you look at the kind of health care reform package and themes that seem to be coming, we will continue to focus more on community-based care, and more on health promotion and disease prevention. We will also look at how we both maintain and improve quality while reducing cost. I think that nursing research can contribute very effectively in those three areas.

We have a very strong health promotion/disease prevention program. About 45 percent of our resources are devoted to health promotion strategies. Our testing of interventions for health promotion run from preventing low birth weight to working with exercise programs for the elderly to reducing falls by enhancing balance and enhancing muscle strength.

We also have a series of projects that look at how one can restructure some of the health care systems so that more home care and community care can be given, thus reduce costs associated with hospitalization.

I mentioned one study earlier in the opening statement in which we have physicians and nurses working together to look at how nurse midwives in particular can take more responsibility for low-risk pregnancies and low-risk births. The preliminary results clearly showed about a 10 percent decrease in costs, while maintaining all of the quality parameters.

We also have research which shows that you can take individuals home from the hospital earlier when they are physiologically stable and are working with clinical specialists and advanced practice nurses in the community. Cost savings are anywhere from 6 percent for women who have had hysterectomies, to 38 percent for women who were diabetic and gave birth. There are some astounding cost differences, and quality indicators are being monitored and maintained.

Mr. HOYER. Thank you, doctor .

Thank you, Mr. Chairman.

Mr. SMITH. Mrs. Bentley, did you not finish?

Mrs. BENTLEY. I have one follow-up question on the subject we were discussing when I left. We were talking about Epstein-Barr.

Dr. FAUCI. Yes.

Mrs. BENTLEY. And I had asked you how they compare with mononucleosis. Would you review that answer again? Then I have a follow-up.

EPSTEIN-BARR VIRUS

Dr. FAUCI. Yes. The EB virus is clearly related to mononucleosis. There is no question about that. Mononucleosis in its most common form is an acute syndrome generally among younger individuals that lasts for a period of anywhere from a week to several weeks, usually with complete recovery.

A very rare group of individuals do not recover, and they go on to develop a neoplastic complication. That, however is very, very rare.

The direct causal relationship between the microbe and the syndrome is very clear and has been very well studied.

Mrs. BENTLEY. Now, what kind of treatment do you recommend or are you at that point yet for Epstein-Barr?

Dr. FAUCI. There really is not very good treatment for viruses in general, but certainly not for this type of virus. It is related to a virus that does have some response to a drug called acyclovir that we generally use to treat the common Herpes virus infections.

The benefit of this particular drug against a true EBV infection is minimal at best. There are still some physicians, because of the similarities of the two, that would use acyclovir but there is no good effective treatment for Epstein-Barr infection.

Mrs. BENTLEY. Does diet have anything to do with it?

Dr. FAUCI. When one says diet, if you are talking about the extremes of malnutrition, many infectious diseases in individuals who are malnourished have a more fulminant if not protracted course because of the weakening of what we call the host responses to it. But diet per se, in the classic sense that we think of as diet, there is no proven connection between diet and acute mononucleosis or EBV infection.

Mrs. BENTLEY. Thank you, Dr. Fauci. Thank you, Mr. Chairman.

Ms. PELOSI. Thank you, Mr. Chairman. Dr. Fauci, welcome. Welcome to all of you once again, Dr. Varmus.

Dr. Fauci, I will begin with you. I want to commend you for all that you have done in leading the AIDS research efforts over the last several years, and wish you well in leading these focused efforts ahead to find out more about how HIV progressively weakens the human immune system.

I wanted to follow up on a question that Mr. Hoyer had about funding for the CDC. I appreciate the concern he expressed about how it affects STDs, but I also wanted to talk about how the prevention money for AIDS being flat funded is a problem too.

What we have been trying to do with legislation in Congress is develop programs to change individual behavior and community norms. The same behavior can lead to HIV as well as to the STDs, so I hope that in your collaborative effort with CDC, that it extends also HIV transmission.

NIAID AND CDC COLLABORATION

Dr. FAUCI. Very much so, Ms. Pelosi. For example, we have what is called the Women's Interagency HIV Study. This is a collaborative effort between the CDC and NIH that is involved in studying the problem of HIV transmissibility in women.

Ms. PELOSI. Well, I wasn't sure I caught exactly what you said to Mr. Hoyer. Do you think the CDC HIV prevention funding is adequate?

Dr. FAUCI. What I told Mr. Hoyer is that we work in tandem with CDC in regard to STDs. If the question is, are there scientific opportunities for basic and clinical science to be exploited, the answer is that the number of scientific opportunities far exceed the available resources. That can be easily translated into we can do more with more.

Ms. PELOSI. Well, I think it is an important place for us to invest resources because, as has been indicated here, there is concern about the finite nature of the commodity we are dealing with, that being money, and we want to hopefully find a cure so that we—but short of that, we have to stop the spread so that we don't have to spend endless money for income support and care.

Dr. FAUCI. There is no question that prevention of HIV transmissibility, whether it is direct prevention behavioral modifications, education, or addressing other areas such as the prevention of sexually transmitted diseases, or treating an infected, pregnant woman to block transmissibility to her infant. All of those things are very important components of a preventive effort. I couldn't agree more.

Ms. PELOSI. I know they are important and they are a good investment because they ultimately save money, but more importantly, they will save lives and improve the quality of life.

Dr. FAUCI. I agree completely.

TOPICAL MICROBICIDES

Ms. PELOSI. Since you mentioned the work that you are doing in terms of HIV infection in women, I will follow up immediately with that. I know the study of HIV infection in women is a major focus of your work. Because virucides are needed as a prevention tool to reduce the risk of STDs, including HIV infection for both men and women, last year this Committee urged NIH to mount a focused and sustained effort to stimulate the development of safe, effective virucides.

Could you describe your efforts to respond to this request, including the funding committed to this effort during the fiscal year?

Dr. FAUCI. Yes, I would be happy to, Ms. Pelosi.

As we discussed last year, we call it the Topical Microbicide Initiative and it is an initiative that is shared in a collaborative way at the NIH level between the National Institutes of Allergy and Infectious Diseases and the Child Health Institute.

In 1994, the combined funding effort of the NICHD and NIAID, was approximately $12 million. We have accelerated that so that in FY 1995, NIAID's funding level of $12.12 million, together with Child Health's $12.7 has now essentially doubled the effort.

The plan is a coordinated plan that has three parallel tracks, ranging from basic science to product evaluation to clinical trials, and we are in the process of implementing that plan now. The requests for applications are now being announced and hopefully we will be able to make awards in early FY 1995.

We are having some difficulty, as all the Institutes have, in the burden of evaluation and shepherding at a time when we have severe constraints on FTEs, but we are making a major effort to get that implemented as quickly as possible. It is a very important effort not only public health-wise, but to produce a mechanism that can empower women to be in control of their fate vis-a-vis STDs in general and specifically HIV. I think this initiative is going to have a major impact, particularly when you look at the shift in the demographics of the HIV epidemic in this country.

The pattern is shifting so that the new infections are seen to a much greater extent now in heterosexual populations, particularly women.

Ms. PELOSI. I appreciate your saying that. Can you assess the potential for a safe and effective over-the-counter spermicide to prevent HIV infection or a non-spermicidal product.

Dr. FAUCI. I think the potential for over-the counter topical microbicides is reasonably well founded. I think it can be done and that we have the potential to make it a reality.

There are several obstacles, one of which I am sure you heard about, is that anything that will topically be able to be put onto a mucous membrane that could kill a microbe has the potential of inflaming those membranes and thereby having the paradoxical effect of enhancing transmissibility. So we need to resolve that aspect and once we get that issue resolved, I think we should be able to make a lot of progress from that point on.

Ms. PELOSI. That is great. As you know, a group called the Future Directions of AIDS Research, or the "Madison Project", has suggested that NIH set aside a small part of Federal funds for AIDS research to invest in a research project to demonstrate a more flexible, more team-oriented management model for drug development.

I know that you participated in some of the meetings and you are even more familiar than some of us are about all of them. In your view, are there alternative models to research management potentially useful in the AIDS research program, particularly as it relates to filling the gaps between basic science and AIDS treatments?

DRUG DEVELOPMENT

Dr. FAUCI. The answer to your question, Ms. Pelosi, are there alternative models, there certainly will always be alternative models. But I think what is not very well appreciated is that the targeted and focused effort in areas such as drug development are, in fact, going on at the present time.

With regard to the management of that, some of the discussion that came up in several of those meetings was centered around managing it a little bit differently. If you look at the complexities of the total NIH research effort for FY 1994, $1.3 billion, there is a substantial amount of those resources that are on a fast track for targeted drug development, including consortia between industry, academia and the government.

A case in point would be the national cooperative drug discovery groups in my institute.

If you did a little bit of semantic twisting around, you could call that almost a Manhattan Project for the development of drugs. I went away from those meetings understanding the concern about wanting to set aside a certain amount of money to do that, but the conclusion I came away with was that given the constraints that we have in resources now and a comprehensive plan that has been developed over the past couple of years, that it would be best suited to proceed according to the plan and the mechanisms that we are doing right now.

Ms. PELOSI. And would that include immune based therapies?

Dr. FAUCI. Absolutely. In fact, that has been one of the highest priorities that our Institute specifically, and the NIH in general, has backed: from the very basic level of finding how the immune system can better control HIV in a person that is already infected to a major growth in enhancement of immune-based therapy, in our extramural and intramural program.

So that is something that has been going on and has been fortified by the recent meetings of our coordinating committees that were held in Bethesda just a few weeks ago. Therefore, you have both NIH staff and extramural support of the immune-based therapy concept.

Ms. PELOSI. Thank you, Dr. Fauci.

Should I save my questions for the next round, Mr. Chairman?

Mr. SMITH. Ms. DeLauro.

Ms. DELAURO. Thank you, Mr. Chairman.

Welcome Dr. Fauci and Dr. Leshner, nice to see you today. I want to associate myself with Mr. Hoyer's comments on HIV prevention activities through the CDC, and also associate myself with the comments of Ms. Pelosi with regards to microbicides. I support those efforts and think we need to continue them.

As I mentioned to you yesterday, these are areas of tremendous interest and I will want to continue conversations about them.

Let me follow up also on another question with regard to AIDS and then move on to Lyme disease, if I might. With regard to the AIDS virus, in recent reports, I was reading that there is now some evidence that the HIV virus itself causes cancer as opposed to just making persons with AIDS more susceptible to various kinds of cancers. Is this accurate, and how does this new understanding affect our ability to treat AIDS or other cancers that are caused by the virus?

RELATIONSHIP OF AIDS AND CANCER

Dr. FAUCI. I think at this point in time, despite the study that recently appeared in the literature, that I do not believe that we can say with confidence that HIV directly causes certain cancers. Let me try to put it in lay terms so you can understand what the experiment demonstrated.

The experiment was built around the premise that there are certain genes that actually are involved in the production of certain types of neoplastic states. Dr. Varmus was awarded a Nobel prize for this discovery.

The hypothesis is that when the HIV gene inserts itself into the host cell genome, it may do so in proximity to a particular gene that is responsible for the initiation of a neoplastic event. If this occurs, you could say that in fact the HIV is directly causing that cell to turn cancerous.

We know from reasonably good studies that HIV, inserts itself randomly into the gene of a cell. In other words, it will just go anywhere.

The study found that HIV can insert itself next to a gene that might cause cancer. However, by chance, this would be a random, and rare, occurance.

Mr. VARMUS. I agree entirely. I have looked at the paper. I think we need more information before we jump to conclusions. It may be that HIV has played a role in a few select cases of special forms of lymphoma, but I think at the moment, it appears to be a fairly rare event and the importance of the event, even in those cases, I think needs to be looked at more closely.

Ms. DELAURO. I am beginning to—given my questions yesterday with regard to telomerase, wonder about the newspaper reports we read on a regular basis about some of these areas and regarding the HIV virus—whether it is causing cancer and so forth.

I say this and I know the answer, too. There seems to be no ability to control some of these stories getting out that really put people in a frenzy or give them such false hopes and expectation. There seems to be no way to get some handle on this.

Mr. VARMUS. There is an unusual relationship between journalists and scientists. I am going to use my forthcoming talk at the National Press Club to address this topic.

Dr. FAUCI. It goes both ways because there is, in many respects, fear that is instilled, and then there is false hope. So it is a roller coaster effect. It is one of the last of the non-peer reviewed disciplines.

LYME DISEASE

Ms. DELAURO. What can we do about that? Let me ask again in follow up to questions of my colleague, Mrs. Lowey, on Lyme disease. Dr. Fauci, you talked about it.

You are continuing with the investigation of whether chronic Lyme disease is an infectious or a post-infectious disorder. How many awards do you anticipate will be made in order to further the research into this question?

Dr. FAUCI. Right now we have 34 peer reviewed projects that have been awarded on this. As I mentioned earlier with regard to the other disciplines, that there is more good science out there on Lyme disease than we can actually fund, and that is what we all have been talking about when asked the question, what do we think is a reasonable award rate.

If we could get our success rate of grants to the 40 percent level, we would capture, I believe, a considerable number of additional worthy grants that are directly or indirectly related to Lyme disease.

As an Institute, we ourselves take Lyme disease as one of our priority areas, so when we have a small amount of money that we can use to selectively pay additional awards in high interest areas, Lyme disease is among those projects considered.

It is the most common vector-borne illness in the United States. So we take it very seriously, and we do want to and can fund more if additional resources were made available.

Ms. DELAURO. In terms of the number of awards, what does that translate into in terms of the amount of money that was spent in 1993 on Lyme disease and particularly on the chronic Lyme disease?

Dr. FAUCI. Most of the research done is on things that overlap acute and chronic. In FY 1994, we estimate about $10 million, and in 1995 we estimate spending close to $11 million.

It would be impossible, Ms. DeLauro, for me to give you a figure for chronic Lyme disease only. But I can tell you that the attention of the biomedical research community is focused on that area because that is one of the most perplexing aspects of Lyme disease.

Ms. DELAURO. The attention and the resources?

Dr. FAUCI. Right.

Ms. DELAURO. I am asking you as a professional, is this—obviously everybody would love to have more money if you could have it, but are we focusing enough money in this particular area?

Dr. FAUCI. I will give you a specific example. Right now we have on the street an RFA, a request for applications, for the immune response to Lyme disease, which focuses on two areas.

One is for the development of a vaccine, and the second, is a request for proposal of contracts on an animal model of chronic Lyme disease. So we are using the available resources to generate interest in developing a model of chronic Lyme disease so that we can really start dissecting this disease.

Ms. DELAURO. Thank you. Thank you very much.

Thank you, Mr. Chairman. I think my time is up.

Mr. SMITH. I just had one question at this point. We have now, as I understand it, a vaccine resistant TB. Is that right?

Dr. FAUCI. Drug resistant tuberculosis, yes.

Mr. SMITH. We depend heavily on vaccines. Down the road, aren't we going to find vaccine resistant diseases really?

DRUG RESISTANT MICROBES

Dr. FAUCI. Well, vaccine resistance is not in the classical sense of what we call drug resistance. There is resistance in the more generic sense in that there are diseases that we are having trouble developing a vaccine for.

Once you get a vaccine to prevent a disease, it is extremely unlikely that with the microbes that we know something about, that you would develop a vaccine-resistant microbe. You try to develop a vaccine that covers the broad range of ways that a microbe would present itself, so that it isn't just specific for one component of it.

But there are two different concepts. There is the emergence of drug resistance and then there is the difficulty for getting a vaccine for certain microbes because they change rather rapidly. HIV is a typical example of a microbe that has a high mutational capability, which is one of the stumbling blocks in developing a vaccine.

Mr. SMITH. We are going to do what we can so that our generation and our succeeding generation can defeat the balance of nature temporarily, but the balance of nature is so powerful that over the years, it has a way of defeating whatever manipulation man does, and in the case of plants, for example, we can develop a herbicide and insecticide that temporarily meets an objective, but one way or another then, there is a new plant that takes its place that is resistant to the herbicide or there is a new insect.

One way or another, the balance of nature beats us. We have got to continue to manipulate it, haven't we?

Dr. FAUCI. I would just make one slight modification to what you said. It doesn't beat us or defeat us, but it mandates that we are on guard all the time, and you just articulated the best reason in the world for the NIH.

Mr. SMITH. We think we have defeated whatever disease it may be, but either that disease will reappear in some other form or else one will take its place.

Dr. FAUCI. Exactly, and it is our job for the survival of our species to use our intellectual capability to try and stay ahead of the race. That is why we are in the research business.

Mr. SMITH. Mr. Porter.

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Leshner, we want to welcome you as a new director. We appreciated very much your work at NIMH and the kind of results-oriented leadership that you provided and will at NIDA.

I want to begin by asking you the same two questions I asked Dr. Varmus yesterday. What is the greatest problem facing, NIDA and what are your greatest challenges as the chief administrator of the Institute?

Mr. LESHNER. I think we have heard today as a part of the discussion that one of the greatest scientific challenges is going to be how to build an infrastructure to have an impact to significantly improve treatment in this country. Among the approaches that we are taking are biologically-based approaches and behaviorally-based approaches, and approaches attempting to bring people back into society.

From an administrative point of view, which is how the question was phrased yesterday we, like the other institutes, are of course faced with resource constraints and are faced with problems surrounding the FTE requirements, so I would just second Dr. Varmus' comments from yesterday in that regard.

DRUG ABUSE RESEARCH OPPORTUNITIES

Mr. PORTER. What are the most exciting recent advances in drug abuse research? What are your opportunities for the year ahead, and is the President's budget adequate to take full advantage of these opportunities. If not, how much additional funding would be required to do so?

Mr. LESHNER. We have talked a bit today about some of the wonderful NIDA-supported discoveries that have occurred in neuroscience and in our understanding of drug abuse as a disease of the brain, and I think we now have the tremendous opportunity to move forward from those discoveries. That is, now that we have recognized receptors in the brain, we have to figure out why we should care about that in terms of clinical reievance, and move to the next level of analysis.

The second set of opportunities that I have—that I think may to some people seem obvious, but to other people counter intuitive—is that we actually have discovered that we can do successful outreach to intravenous drug abusers and affect their AIDS-related behavior. That finding by itself could have tremendous public health implications, and so it is an area that we will be working substantially further in.

Mr. SMITH. We are going to have two votes this time.

Mr. LESHNER. There are a range of scientific opportunities, which I outlined in my testimony, so I won't take your time in going through some more of those at the moment. But on the other question that you asked, again, I will repeat a response that Dr. Varmus gave yesterday. We think that an appropriate success rate for our Institute would be around 40 percent. The President's budget request does give us a very good start towards that. To achieve that level would require a substantially larger increase in the range of 36 percent.

Mr. PORTER. One-third of your budget is dedicated to AIDS research. Given the opportunities available in AIDS research and non–AIDS research, is this an appropriate balance?

Mr. LESHNER. For us right now, it does appear to be an appropriate balance. The very large prevalence of intravenous drug use as a spreader of AIDS makes the intersection between AIDS and drug abuse a very important one, and in fact our major contribution ultimately to the AIDS epidemic surely will in large part be to improve drug abuse treatment and to get people into treatment.

The recent finding that HIV zeroconversion rates in the populations that are in methadone treatment are markedly lower than in those out of treatment is very important and significant. So we have had a reasonable balance between the AIDS and Non-AIDS portions of the budget.

AIDS SUCCESS RATE

Mr. PORTER. The budget on page 27 of the overview states that in 1994 you had a success rate of 95 percent AIDS research as compared to only 20 percent for non–AIDS research.

Mr. LESHNER. No, I think the AIDS success rate has been in the range of 40 percent.

Mr. PORTER. Why don't we look at page 27? Yes, it shows 95 percent and 20 percent, and 31 percent overall.

Mr. LESHNER. Excuse me while I consult. I hadn't seen that. There was evidently a straight line estimate of the number of AIDS applications that we would receive. Our own subsequent projections, since the budget was prepared suggest the success rate it is closer to 41 percent.

Mr. PORTER. All right. I was going to say that if it was 95 percent, that that is troubling to me, especially in view of 20 percent for non–AIDS research, and it is more like 45 percent?

[EDITOR'S NOTE.—The following information was provided by the witness subsequent to the hearing:]

The AIDS success rate at NIDA is 41 percent. In addition to AIDS applications identified by the office of AIDS Research for the purpose of expedited review NIDA considers a portion of treatment and outreach research with injecting drug users and crack cocaine users to be related to the AIDS epidemic and this results in a lower success rate calculation.

Mr. PORTER. Are we missing any opportunities on the non–AIDS side with the 20 percent success rate as opposed to 45 percent success rate on AIDS?

Mr. LESHNER. Well, of course, but I don't think it is at the expense of the AIDS success rate. The truth is we have very many AIDS-related grants that we aren't able to fund. We would love to be able to fund. We are missing opportunities by not having the resources to bring us generally up to about a 40 or 45 percent success rate overall for all drug abuse research.

Mr. PORTER. Dr. Hinshaw, we want to thank you for your service at NIH. We are very sorry to lose you. You have steered the Nursing Center through a very difficult transition to Institute status and if you weren't going to one of my alma maters at the University of Michigan, I would be very upset.

Dr. HINSHAW. Thank you, sir.

NINR SUCCESS RATE

Mr. PORTER. I have a couple questions. The grant award success rate for NINR has been far below the average at NIH. This year it is only 10 percent. Even next year your success rate is estimated to be only 19 percent. That seems far too low. What would it take to bring your success rate up to that of NIH's average?

Dr. HINSHAW. Actually the success rate for 1995 is projected to be 12.2, which is even worse. We have been very concerned about this, as is NIH, and we have had a number of consultations.

All of us are looking at constraining resources. To increase our success rate from 12.2 percent to the NIH average, which is 27 percent, would require about an additional $13.5 million.

In the meantime we will try to conduct collaborative research programs with other ICDS that will leverage our money upward. What we are most concerned about, however, is the scientific opportunities that are being lost as a result of the low success rate.

RESEARCH TRAINING

Mr. PORTER. Well, 12 percent is way too low and progress from only 10 to 12 percent over that period of 1994 to 1995 is also too slow, so we certainly have to give some attention to that. In 1991 the NINR had 269 full-time training positions. That number is decreased to 208 in 1994 and remains constant under the budget request.

Why have you experienced this drop in training slots and what is an acceptable number of slots in your professional opinion?

Dr. HINSHAW. There are essentially two reasons why we have dropped. One is that training costs have increased, such as tuition levels and stipends. While we recognize the importance of these increases, they do impact on the numbers of trainess that can be supported. We currently have about 8 percent of our resources invested in research training compared with the NIH average of about 3.3 percent. That is because we have a very new, young, growing scientific community that really needs the support from an investment in research training.

A second factor is that we have shifted some monies from predoc into postdoc awards. While this represents a relatively small amount of money, the higher costs of postdoc awards result in fewer total awards being made.

You asked what would be a reasonable number of trainees to support in my professional judgment. The community, through the Biomedical and Behavioral Personnel Committee at IOM, has been suggesting that we should be supporting somewhere around 350 full-time training postions at this point in time, and close to 500 by 1996. I support these recommendations.

Mr. PORTER. Dr. Hinshaw, thank you very much, and we wish you good luck at Michigan.

Dr. HINSHAW. Thank you.

Mr. SMITH. Ms. Pelosi.

Ms. PELOSI. Thank you, Mr. Chairman.

I have questions both for Dr. Leshner and for Dr. Hinshaw, but in the interest of time, I would like to submit them to the record, welcoming Dr. Leshner, wishing him much success and bidding farewell to Dr. Hinshaw and wishing her much success.

Dr. Leshner, for your information, my questions will relate to a drug-free school program and how you are involved in evaluating the outcome of the drug abuse prevention program.

And Dr. Hinshaw, my questions for you relate to breast cancer and to how nursing research is looking at how to assist individuals and families facing this situation and also how nursing research is currently being funded and what the plan is in regard to symptom management with individuals with HIV disease.

You don't have to answer now, but I did want those questions on the record and thank all of you for your testimony today.

You too, Mr. Williams.

Thank you, Mr. Chairman.

Mr. SMITH. Thank you all very much.

[The following questions were submitted to be answered for the record:]

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

AIDS

Mr. Smith: A number of recent articles has questioned whether there has been sufficient progress in developing AIDS vaccines to move any into Phase III clinical trials. What is your view of the state of science in AIDS vaccines, and what process is in place to make the judgment about moving to the next phase of testing?

Dr. Fauci: Because clinical trials of only the most promising vaccine candidates can be supported by the NIAID and because volunteers are a precious resource, careful selection of candidate vaccines to be entered into clinical trials is necessary. On April 21 and 22, a HIV Vaccine Working Group (VWG) from NIAID met to evaluate whether or not the current scientific data warrant expanding clinical trials of one or both candidate HIV vaccines that are furthest along in development. The VWG, formed by NIAID in December 1992, is a group of government and non-government scientists and community representatives that meets periodically to review the status of HIV vaccine research, define the scientific questions most important to moving the field forward and determine the research needed to address these questions.

Both candidate vaccines evaluated by the VWG at the April meeting contain genetically engineered versions of the major HIV envelope protein, gp120. The vaccines are based on two different but closely related HIV-1 strains representative of most infections in North America and Europe. Biocine (a joint venture of Chiron and CIBA-Geigy, Emeryville, California) made their vaccine from the SF-2 strain; Genentech, Inc. (South San Francisco) based their vaccine on the MN strain. Currently, these are the only experimental HIV vaccines being evaluated in Phase II NIAID-sponsored preventative vaccine clinical trials.

After careful consideration, the vast majority of the VWG agreed that there are no additional laboratory or animal model data that will significantly add to the knowledge base about whether a recombinant gp120 candidate vaccine might afford protection from HIV infection. They concluded that the scientific rationale supports advancing and expanding clinical trials to evaluate this hypothesis. Such trials would be incorporated into a broader prevention effort that includes frequent counseling of trial volunteers to avoid HIV infection.

In mid-June, representatives of the VWG will present their assessments and a proposed trial design to NIAID's AIDS Research Advisory Committee (ARAC) and the AIDS subcommittee of the National Advisory Allergy and Infectious Diseases Council. Its members represent a wider variety of AIDS research and patient concerns than the VWG and can provide a broader perspective on expanding clinical testing of these vaccines. Following the advice of these groups, the Institute will decide how to proceed.

As these discussions evolve, clinical evaluation of other experimental products will continue to be an essential component of NIAID's mission to facilitate research and development of an effective AIDS vaccine. NIAID will continue to monitor and re-evaluate the state-of-the-art in HIV vaccine development and consider moving other candidate vaccines into expanded clinical studies as more information on them becomes available. Significant developments concerning any viable preventive approach may lead to appropriate changes in the direction or scope of NIAID's commitment to a specific candidate HIV vaccine or alternative preventive strategy.

Mr. Smith: Do you think testing of vaccines is further away than you have predicted in past years?

Dr. Fauci: The development of a safe and effective vaccine to prevent HIV infection and/or modulate disease is of high public importance. Though one always wants research to move ahead as quickly as possible, I am pleased that significant progress has been made in the development and clinical testing of potential candidate vaccines. To date, 12 separate HIV antigen preparations have been or are being evaluated in NIAID trials. Currently, 38 Phase I and II trials of these preparations, alone and in combinations, have been developed.

Mr. Smith: Last December *Science* magazine ran an article describing a new goal in AIDS vaccines of preventing disease rather than achieving sterilizing immunity. Have you shifted your focus in vaccine development to this strategy?

Dr. Fauci: NIAID's plan for vaccine development and efficacy trials has not been altered by animal model results to date. The *Science* article was based on a preliminary assessment of simian immunodeficiency virus (SIV) animal model studies, as presented at a NIAID-sponsored vaccine meeting.

SIV causes an AIDS-like illness in certain species of monkeys. The assessment suggested that vaccinated monkeys not protected from SIV infection may live longer than non-vaccinated SIV-infected monkeys. A more careful analysis of results with several leading vaccine designs suggests that there was no statistically significant difference in survival in vaccinated/infected versus non-vaccinated/infected animals. Analysis of animal studies in which newer vaccine designs were used is in progress.

Regardless, animal model studies may or may not be indicative of efficacy in humans. Efficacy trials in humans will be required to determine if a specific product protects humans from either infection or disease. During the course of the efficacy trials, NIAID will monitor whether volunteers become infected and for those who do become infected, the extent to which HIV remains after the initial months of their infection. In addition, as a secondary outcome, volunteers who become chronically infected will continue to be followed to determine if disease is prevented or altered by vaccination.

Mr. Smith: Over time, do you hope to change the balance in your research portfolio between therapeutics for those already infected with HIV and drugs to prevent infections altogether?

Dr. Fauci: The mission of the NIAID in the field of AIDS research has three major components: (1) to support basic biomedical research in scientific disciplines that can provide fundamental knowledge about HIV disease and its sequelae; (2) to facilitate the discovery and development of therapies for HIV infection and its complications; and (3) to facilitate the discovery and development of an effective vaccine. NIAID has a strong commitment to all of these components. The balance between one area and another is influenced primarily by research and scientific opportunities in the context of available resources.

Mr. Smith: Is a large share of your AIDS budget in the "continuation" category in 1995? Does this change substantially in 1996 when the AIDS adult clinical trial units are up for renewal?

Dr. Fauci: The FY 1995 dollar commitments for research project grants (RPG), which include the adult AIDS Clinical Trials Units (ACTU), constitutes about 77 percent of the total FY 1995 RPG budget.

The adult ACTUs will be recompeting in FY 1996. These units will have to compete with all of the other new and renewing AIDS initiatives NIH-wide. The NIAID, along with all of the other components of the NIH, will be submitting an FY 1996 AIDS Budget Request to the NIH Office of AIDS Research (OAR), which will include requests for new and renewing AIDS projects. Because of the NIH Reauthorization Act, the OAR will have the responsibility of determining the funding of these requests. The OAR will prioritize and provide funding for as many projects as they can based on the dollars appropriated by Congress. The number and amount of funding for the adult ACTUs will be determined by the OAR based on where they fall on the OAR priority list.

Mr. Smith: With the benefit of several years hindsight, do you feel we have maintained a proper balance in AIDS clinical trials between adult and pediatric cases?

Dr. Fauci: With the resources at our command, we feel that we have maintained a proper balance between our adult and pediatric clinical trials.

Mr. Smith: In your judgment as the past AIDS Office Director, do you think a Manhattan Project-style approach to AIDS is likely to be successful?

Dr. Fauci: Most biomedical researchers feel that the science of HIV is not far enough along to mount a true "Manhattan Project." Creating a central location for AIDS researchers to search for a cure is not yet a viable scientific endeavor. Manhattan-like projects that fund a small group of investigators to focus their scientific efforts on a particular research question may be a more practical alternative. Initiating such a program would require an additional investment of funds, or the redirecting of funds from ongoing projects. It would be more important not to divert funds from worthy ongoing research in order to embark upon a directed project of uncertain benefit.

INTRAMURAL RESEARCH

Mr. Smith: You have the reputation for being a good manager of your intramural research program. What principles guide your management of the intramural operation, and how do you review its performance?

Dr. Fauci: The NIAID employs a number of mutually reinforcing approaches to manage and review its intramural research program. The process is ongoing, and it involves our National Advisory Allergy and Infectious Diseases Council (NAAIDC), our Board of Scientific Counselors (BSC), external review panels and task forces, the Congress, and NIAID's internal planning process. An overriding goal of the NIAID process is to ensure that we rapidly respond to a changing scientific environment within the resources available, while using the most appropriate mechanisms possible.

The Director of the NIAID Intramural Research Program briefs the NAAIDC each year on the research conducted by intramural scientists. As part of this briefing, the NAAIDC reviews the Intramural Research Program and the results of intramural site visits conducted by extramural scientists. Intramural scientists provide presentations on their research to the program advisory subcommittees of our NAAIDC. Also, we have asked members of our NAAIDC to participate in the site visits conducted of our intramural laboratories.

During the fiscal year, our NAAIDC discusses the relative balance between our intramural and extramural programs to ensure that the balance is appropriate for the research supported by the NIAID. The NAAIDC members have consistently concurred with the allocation of resources between intramural and extramural research.

The NIAID BSC conducts an in-depth review of each NIAID laboratory. The BSC is composed of acknowledged leaders in the fields of allergy, immunology, and infectious diseases and is supplemented with ad hoc members to provide added expertise in particular areas. The BSC review considers the scientific program of each laboratory as a whole, evaluating the quality of the laboratory's leadership and the relevance of the laboratory's focus to the major research issues in its field. The BSC also evaluates individual scientists, from the senior scientists to the post-doctoral fellows, with respect to the areas of leadership, quality of the research questions being asked, and the research productivity. The BSC evaluates the resources of the laboratory, including the contracts associated with the laboratory and the laboratory space allocations. Additionally, the BSC considers the progress of tenure track candidates and provides advice and consent on whether such candidates should be formally considered for tenure. The BSC provides both oral and written comments and advice to the NIAID, and the NIAID takes action based on this advice.

We rely on a number of panels and task forces to provide us with advice on the scientific aims and goals to pursue the appropriate balance between intramural and extramural research. These task forces and panels, comprised of extramural scientists, help to frame NIAID's future research agenda, identify scientific projects, and indicate which projects would be most appropriately conducted intramurally.

For example, the NIAID convened a Blue Ribbon panel to assess the state-of-the-art in tuberculosis (TB) research and provide the Institute with advice and guidance in this area. The panel was comprised of extramural and intramural scientists who identified areas of research that should be stimulated and who supported the Intramural Research Program's launching of those projects that needed a quick response, such as drug development and clinical testing for multi-drug resistant TB. This ability to be a "strike force" capable of responding rapidly to public health crises is the hallmark of the Intramural Research Program.

Recently, the NIAID convened a panel to assess the state-of-the art in vaccine development research. This panel identified numerous scientific areas that the NIAID should pursue and concurred that the Intramural Research Program was positioned to begin pursuing some of the research goals immediately.

Another example is a recently convened panel that provided advice on how the NIAID should spend additional funds on AIDS research for FY 1994 and to guide us in deciding the balance between intramural and extramural research. Our National Advisory Allergy and Infectious Diseases Council and AIDS Research Advisory Committee provided advice and guidance on a plan to spend additional AIDS research funds and concurred that certain aspects of the plan were best suited to be conducted through our Intramural Research Program.

On occasion, the Congress identifies our Intramural Research Program as an appropriate vehicle for stimulating research in a particular area. For example, the Congress concluded that the NIAID should double its intramural AIDS outpatient clinical trials effort and rapidly expand studies of Lyme *borreliosis*. The strike force concept was confirmed by the Congress in that they actually identified the Rocky Mountain Laboratories as the most appropriate site to conduct Lyme *borreliosis* research.

The NIAID internal planning process is an ongoing procedure geared towards two Institute-wide reviews of policies, procedures, and research initiatives. The process begins two years in advance of the fiscal year that is being considered. The first phase of this process occurs in the winter; it provides a forum for NIAID senior management and scientific staff to discuss and identify future scientific directions and research priorities in broad, philosophical terms and spurs discussions regarding NIH/NIAID policy issues and special problems. These discussions help guide the development of specific intramural and extramural research initiatives, both new and recompeting, that will be discussed during the second phase of the process known as our Summer Program Review. The Summer Program Review is designed to provide a forum to:

- Allow information exchange across NIAID Divisions (intramural and extramural) by informing the Division Directors about each other's priorities;
- Provide advice to the NIAID Director regarding the Institute's scientific priorities;
- Create a collective decision-making process regarding NIAID initiatives--which is now more important in light of tighter budgets;
- Provide input to the Division Directors for the development of their research initiatives; and
- Reach a consensus on Institute priorities before investing or reinvesting limited dollars.

Central to the discussion of each proposed research initiative considered during this review is the appropriate focus of the initiative, whether the proposal would be best carried out intramurally or extramurally, and the level of funding. For example, discussions might determine that a research initiative proposed by an extramural Division would be best carried out intramurally or through a collaborative effort with the intramural Division.

In addition to the Institute-wide NIAID planning process described above, the NIAID Director reviews the budget of the various intramural laboratories and the percent of the budget devoted to personnel, travel, supplies, and equipment. Throughout this process, the NIAID Director stresses the importance of minimizing the cost of conducting intramural research and requires justifications for cost increases exceeding inflation. Also, as part of this review, the NIAID Director reviews the research priorities of the intramural laboratories.

Prior to review by the NIAID Director, each intramural laboratory is required to submit an annual budget to the Director of the Division of Intramural Research, where proposed projects are critically reviewed to ensure that the amount provided to each laboratory is consistent with the overall increase anticipated for ongoing research.

The fundamental conclusion is that the management and review of NIAID's intramural research program is determined through both an established and ongoing internal planning process and with guidance from advisory groups and ad hoc panels of outside experts. The decision making process is a collaborative effort between NIAID staff and extramural advisors.

Mr. Smith: Have you ever shut down lower priority labs to make room for new initiatives?

Dr. Fauci: Yes. The NIAID has closed lower priority laboratories to launch new initiatives. Assessments drawn from the external and internal reviews described above bear on decisions regarding funding individual laboratories and individual scientists. Past reviews have resulted in the contractions of some laboratories and the closing of others.

In response to BSC reviews over the past few years, the NIAID has closed one laboratory and six sections, which are comparable to divisions in a university, and six tenured scientists were released.

Mr. Smith: Do you think the retrospective review of intramural research is as rigorous as the prospective peer review extramural grants undergo?

Dr. Fauci: We believe that the NIAID's intramural research review process is just as rigorous as the prospective peer review extramural grants undergo. As described above, the NIAID review process ensures both a prospective and retrospective review. The NIAID internal review process ensures that all future research is reviewed by non-intramural scientists. Furthermore, since the Board of Scientific Councilors (BSC) is composed of senior extramural scientists who are leaders in their respective fields, we believe the quality and quantity of intramural's ongoing and future scientific output is being compared with that of laboratories in the extramural community.

The BSC review involves an in-depth and comprehensive evaluation of the quality of work that has been and is being conducted. Thus, any weaknesses in the ideas or structure of the laboratories under review become apparent. Moreover, during the BSC review, intramural researchers discuss future research plans. Thus, the review is not entirely retrospective. In summary, the NIAID's intramural review process is just as demanding as the extramural peer review process. The stature of the individuals conducting the review ensures that intramural researchers are reviewed comparable to extramural researchers; the comprehensive manner in which each scientist under review is examined ensures that all facets of ongoing and future research are assessed, and the reviews incorporate both retrospective and prospective research.

SINGLE VACCINE FOR CHILDHOOD IMMUNIZATIONS

Mr. Smith: Recent news stories have described the prospects for developing a single vaccine for all childhood immunizations in the next five to ten years. Is this timetable feasible, and what has been your Institute's involvement in this worldwide effort?

Dr. Fauci: The Children's Vaccine Initiative (CVI) is a global program with the goal of accelerating the transition to safe, affordable and heat stable vaccines that can protect children against the major infectious childhood killers with few doses given orally early in life, by facilitating the development, production, technology transfer, procurement and introduction of the new vaccines.

The development of a single children's vaccine is an ideal unlikely to be reached within a single decade, but interim successes are possible. The global vaccine research and development community does have within its reach the capability to develop safe and effective vaccines that will simplify immunization schedules, expand the number of childhood diseases for which vaccines are available, and assure the continuing safety of childhood vaccines.

NIAID, as the lead PHS agency for vaccine research, was an early participant in this initiative and has remained active both in terms of the NIAID research program and collaborations with the global efforts. NIAID initiatives in the CVI are carried out under the following assumptions: first, that basic research is an essential component in support of vaccine development; second, that the infrastructure required to accelerate vaccine research and development can be a rate-limiting step; and finally, that research efforts must be focused on promising aspects of vaccinology. NIAID's support of the CVI focuses on enhancing the capability to evaluate candidate vaccines, development of novel immunization strategies, improved vaccine efficacy, and development of strategic alliances with industry and other government agencies.

PROJECTED SPENDING

Mr. Smith: Identify 1993-1995 projected spending for the following: Lyme disease, Chronic Fatigue Syndrome, vaccine development, tuberculosis, sexually transmitted diseases, asthma, virucides, and AIDS clinical trials (with a subtotal of pediatric clinical trials).

Dr. Fauci: The following table displays the information for the requested disease areas for FY 1993 through FY 1995.

	FY 1993 Act.	FY 1994 Est.	FY 1995 Req.
Lyme Disease:	7,948,000	10,302,000	10,640,000
Chronic Fatigue Syndrome:	3,841,000	4,000,000	4,131,000
Vaccine Development:	142,668,000	182,870,000	192,988,000
Tuberculosis:	20,757,000	27,958,000	32,958,000
Sexually Transmitted Diseases:	52,743,000	53,798,000	57,562,000
Asthma:	13,120,000	12,858,000	13,280,000
Microbicides/Virucides:	4,620,000	5,370,000	12,110,000
AIDS Clinical Trials:	176,060,000	196,196,000	203,558,000
Pediatric Clinical Trials:	122,938,000	140,182,000	145,332,000

RESEARCH CENTERS

Mr. Smith: Identify the number, type, and subject matter of research centers supported in 1994.

Dr. Fauci: In FY 1994 the NIAID will fund a total of 15 non-AIDS and AIDS research centers. In addition, we will support seven Research Centers in Minority Institutions. The following is a program description of these centers:

NON-AIDS RESEARCH CENTERS

Tropical Medicine Research Centers (TMRC)

The TMRC program supports research of direct relevance to the health of the people in tropical countries and promotes collaboration and exchange of information between foreign and American scientists. Additionally, the TMRC program serves to strengthen the research capacity of the host countries, enhancing their ability to recognize and contain disease outbreaks. The TMRCs currently perform studies on leishmaniasis, leprosy, malaria, and schistosomiasis.

AIDS RESEARCH CENTERS

Centers for AIDS Research (CFAR)

The very nature of the HIV epidemic requires a multifaceted approach to research that involves basic, preclinical, clinical, and applied scientific investigations. The NIAID CFARs foster interdisciplinary cooperation between basic and clinical scientists who have earned outstanding reputations in HIV and AIDS research.

Each CFAR is organized into core areas reflecting the research priorities and capabilities of the Institution. The cores are responsible for providing support including space, equipment, personnel, and technical expertise to many individually NIH-funded scientific projects in a given research area, such as molecular biology or animal studies. Funds also may support initial salaries and research costs of scientists new to AIDS research and pilot investigations whose feasibility has not yet been proven.

The CFAR concept permits a greater quantity and quality of HIV and AIDS research than would be possible with the same investment of resources in individual grants.

Association of Minority Health Professionals Schools (AMHPS)

The AMHPS is a consortium of historically Black colleges and universities which includes four medical schools, three schools of pharmacology, and a school of veterinary medicine. The AMHPS award is designed to facilitate the consortium's participation in HIV studies in minority populations. Studies under the epidemiology and prevention segment within this grant will contribute to expanding our knowledge about the epidemiology of HIV infection in minority populations and will enable us to better understand the issues related to prevention behavior and high-risk behavior.

Research Centers in Minority Institutions (RCMI)

The NIAID participates in co-funding the AIDS Infrastructure Initiative of the RCMI program, which is managed by the National Center for Research Resources.

The RCMI program is designed to expand the physical facilities and faculty competence in virology, immunology, molecular biology, and the neurosciences so that minority institutions may join the mainstream research on AIDS. These institutions are located in areas in which the AIDS epidemic has hit the hardest, and they are uniquely suited to treat and accrue patients into AIDS clinical trials.

CHRONIC FATIGUE SYNDROME

Mr. Porter: Dr. Fauci, I want to thank you for personally meeting with my staff earlier this year regarding Chronic Fatigue Syndrome (CFS). I am encouraged by your activity on this disorder and hope you will continue the progress in 1995. Would you briefly summarize the activity on CFS?

Dr. Fauci: NIAID's support for Chronic Fatigue Syndrome (CFS) research continues to grow and is expected to reach $4.0 million dollars by the end of FY 1994. Two new grant awards will bring our extramural CFS portfolio to ten research project grants and three cooperative research centers. Several new pilot projects also have been funded through the cooperative research centers program. We are studying this illness from almost every angle, including immunologic, virologic, neurologic, endocrinologic, physiologic and behavioral aspects, as well as trying to elucidate if there is an etiologic agent involved.

To maintain this research momentum, NIAID is announcing a recompetition for our CFS Cooperative Research Centers funding and has joined with the National Institute of Mental Health in preparing a Program Announcement for CFS research on etiology, pathogenesis, and natural history that encourages the submission of proposals for small exploratory projects.

There has been an advance in elucidating the role of cytokines in CFS symptom expression. One of our CFS grantees has shown that there are marked differences in cytokine secretion in men and women, and in women at different times during their menstrual cycle. This is an important area of clinical research that has received little attention. Recognition of gender and biologic cycle-specific differences in the levels of mediators of immunity will not only advance our understanding of why many immunologic diseases occur more often in women than in men, but also will help us to design better case-control studies of immune function.

NIAID has also conducted two scientific workshops. The first was the Second Annual NIAID CFS Cooperative Research Centers meeting, which focused on circadian rhythms in evaluation of immunologic and neurophysiologic tests. The second workshop, organized by the NIAID, the National Institute of Mental Health, and the NIH Office of Research on Women's Health, was held in November 1993 and dealt with the clinical management of CFS. Input from several CFS constituency groups was helpful in the development of the agenda, and participation of patients and their representatives enhanced the value of the workshop. The proceedings are being summarized for publication.

Finally, a leader of the CFS constituency has been appointed to our National Advisory Allergy and Infectious Diseases Council. This member's advice and presence will be invaluable in setting research priorities and will assure that we remain in touch with the concerns of the CFS community.

STAFFING REDUCTIONS

Mr. Porter: How many FTEs will NIAID lose under the budget, and what impact will the cut have on the research, operations, and recruitment strategy of the Institute?

Dr. Fauci: From FY 1993 through FY 1995, NIAID will have lost 96 full-time equivalent (FTE) positions as a result of efforts to reduce the civilian workforce. The loss of FTEs and the targeted reductions to positions in grades GS-14 and above will mean that various recruitment efforts will be constrained. It certainly will have an impact on our efforts to enhance the diversity of our Institute's managerial workforce in terms of minorities--especially African Americans and Hispanics--and in meeting the racial diversity enhancement goals for identified position series that are contained in the recently expanded NIH recruitment program.

These reductions will also affect the Institute's ability to respond to changes in scientific direction and our ability to attract young scientists into our Intramural Program. New areas of research--vaccine delivery methods, i.e, "naked" DNA, gene manipulation and organ transplantation--will be impacted. The loss of FTEs could also affect our regulatory and legal responsibilities as an Investigational New Drug sponsor and our oversight responsibilities, as it relates to clinical trials. NIAID will attempt to meet these challenges by being creative in our approach to managing these issues.

ENROLLMENT OF MINORITIES IN AIDS CLINICAL TRIALS

Mr. Stokes: As you know, AIDS disproportionately affects minority populations. What progress has your Institute made in increasing the participation of minority populations in its therapeutic clinical trials? What major steps has the Institute taken to involve minority institutions in its AIDS clinical trials network?

Dr. Fauci: The participation of specific populations in NIAID-funded clinical trials reflects the changing demographics of HIV infection and AIDS. This illness initially affected homosexual and bisexual men but is currently pandemic, with increasing incidence in women, children, adolescents, injection drug users, and minority populations. Enrollment of underrepresented populations is a high priority in NIAID-sponsored studies. Specific activities in this area include the Terry Beirn Community Program for Clinical Research on AIDS (CPCRA), which has dramatically increased NIAID's enrollment of underrepresented minorities and women in HIV therapeutic trials; establishment of AIDS Clinical Trials Units (ACTUs) at four minority institutions located at Howard University (Washington, D.C.), Meharry Medical College (Nashville, TN), University of Puerto Rico (San Juan), and the University of Hawaii (Honolulu); establishment of Women's Health Committees within the AIDS Clinical Trials Group (ACTG) and CPCRA organizations; provision of supplements to the ACTG for outreach activities toward these populations; implementation of institutional evaluations of progress in achieving recruitment goals at ACTG and CPCRA sites to ensure participation of underrepresented populations; ongoing commitment to the establishment of community advisory boards for each ACTG and CPCRA site; and establishment of NIAID's AIDS Research Advisory Committee task force on underrepresented populations in clinical trials.

MICROBICIDES

Mr. Stokes: What hope does the use of topical microbicides offer for the treatment of sexually transmitted diseases?

Dr. Fauci: For the most part, topical microbicides are being thought about in the context of topical disinfection, that is compounds that interfere with the early steps of the infectious process. Although it is theoretically possible that this approach could be used to deliver drugs to infected mucosal cells, little is known about this at the current time. Although the vaginal administration of anti-retroviral drugs, including nucleoside and non-nucleoside inhibitors of the viral reverse transcriptase, could in theory be useful in preventing HIV replication, it would necessitate knowing a great deal about the chronology and natural history of this infection. We must consider the limited value that some of these drugs might have when used as systemic agents - in terms of their toxicity, poor bio-availability or the emergence of drug-resistant HIV strains - that may not necessarily be experienced to the same degree if they are used as vaginal agents.

AIDS

Mr. Stokes: We have heard so much about the study supported by NIAID that may prevent the transmission of the AIDS virus from mother to infant. Will you tell us about the significance of that research and the role that basic research played in it?

Dr. Fauci: ACTG 076 was a randomized clinical trial of AZT (zidovudine) to prevent HIV transmission from infected mothers to their infants. The treatment regimen that was compared to placebo consisted of AZT administered to HIV-infected pregnant women beginning between 14 and 34 weeks of gestation, continued through delivery, and then administered to their infants during the first six weeks of life.

The development of this protocol was based on knowledge gained through basic research. Animal models of retroviral infection suggested that AZT and other agents may be active as a means of preventing infection after challenging or altering the course of infection. Specifically for this study, preclinical studies in both rats and rabbits found AZT to be nontoxic to the fetus at doses comparable to those that could be used in the clinic.

Examination of the interim results of ACTG 076 by an independent Data Safety Monitoring Board on February 17, 1994, revealed striking results. The findings from the study indicated a 67 percent reduction in the transmission of HIV from the pregnant mothers to their infants when the mother received AZT during the pregnancy and the infant was treated for the first six weeks of life.

There were no significant short-term side effects to either mothers or infants resulting from AZT use other than mild anemia in the infants, which reversed shortly after treatment ended. There is no information regarding any long-term effects on the infants or mothers treated in this study.

The results of this study are directly applicable only to women who initiate AZT treatment between the 14th and 34th weeks of pregnancy, receive no other antiretroviral treatment during the current pregnancy, have baseline CD4+ lymphocyte counts greater that 200 cells/mm3, and have no clinical indications for maternal antepartum AZT therapy.

The PHS has established a Task Force that will be meeting this Spring to further explore the scientific, policy, and financial issues related to these results.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy? Elaborate briefly.

Dr. Fauci: There are many important opportunities to utilize the procedure of gene therapy to treat or prevent human diseases. The diseases of highest priority with the NIAID are primarily those for which the required technology is better developed. The following outlines those disease areas:

Treatment of Non-AIDS Immune Deficiency Diseases

There are numerous genetic diseases which affect the immune system and result in immunodeficiency. Immunodeficiency syndromes are characterized by an unusual susceptibility to infections, sometimes associated with autoimmune phenomena, anemia, low platelet counts, arthritis, malabsorption and diarrhea, and certain malignancies of the lymphoid organs. While each of these diseases is relatively rare, in the aggregate they account for significant human suffering and medical costs.

Some immune deficiency diseases are caused by defective genes, and recent research has focused on the identification and isolation of such defective genes as the essential first step preceding early clinical studies for the replacement of a defective gene with a normal gene. For example, three defective genes which cause immunodeficiency have been identified and characterized in the last year. NIAID supported the work which identified two of these genes: X-linked Agammaglobulinemia, an inherited male immunodeficiency resulting from a defective gene on the x-chromosome and resulting in recurrent bacterial infections, and X-linked Hyper-IgM Syndrome, another inherited male immunodeficiency resulting from a defective gene on the x-chromosome and causing recurrent bacterial infections, autoimmune diseases, and lymphoproliterative diseases. Isolation of these causative genes is an important step in the development of gene therapy for these diseases.

In addition, NIAID-supported researchers have successfully used gene therapy in mice to correct metabolic immune deficiencies through the transfer of non-defective genes. Similarly, NIAID-supported investigators have characterized the defect for one form of Severe Combined Immunodeficiency, an abnormal regulatory gene whose identification will possibly lead to gene therapy to correct this problem.

Genetic Immunization

Several recent studies in laboratory animals have demonstrated considerable success in inducing protective immunity by use of "naked DNA" as vaccines introduced into the skin or muscle cells. The particular attributes of this approach are its simplicity, the ease of preserving and transporting the vaccine, and the need for only a single injection rather than several.

Gene Therapy for Protection Against Microbial Infection

The respiratory and gastrointestinal systems are the major routes of microbial infection in humans. The introduction of appropriate genes, or cells carrying those genes, into the mucosal lining of the airway or gut could prevent microbial invaders from gaining access to the mucosae. For example, genes could be introduced into the cells of the mucosae to block the attachment of microbes. Given the recent re-emergence of microbial pathogens that are resistant to antibiotics, such as tuberculosis, these approaches have become increasingly important to support.

Gene Therapy to Control/Modulate Undesirable Immune Reactions

The rationale for this approach lies in the ability to transfer genes that will produce molecules capable of serving as decoys, and therefore, diverting the course of undesirable immune responses. This technology has potential applicability to a broad range of immune system disorders including autoimmune and allergic diseases. It is also applicable to the prevention of rejection of transplanted organs and tissues, e.g., kidney and heart. NIAID is supporting pre-clinical research to develop further gene therapy techniques for use in the treatment of asthma, rheumatoid arthritis, and multiple sclerosis.

Gene Therapy for Restoration of Immunity to HIV Infection

Three promising approaches to dealing with HIV infection involve the transfer of specific genes. First, there is the possibility of introducing foreign genes that prevent HIV production into hematopoietic stem cells. These stem cells generate all types of human blood cells, including those which protect against infection and are destroyed by the HIV virus. Such modified stem cells would be inoculated into AIDS patients to replace the cells of the immune system with HIV-resistant cells, and thus, could provide a vigorous immune response against the virus. Second, it has been proven possible in model laboratory systems to introduce genes into cells that result in inhibiting synthesis of HIV components or interfering with the assembly of the components. As a result, viral replication is prevented and the infection is stopped. Third, by introducing cultured cytotoxic cells that are capable of killing HIV-infected target cells, it is possible to prepare hyperactive, cytotoxic cells which, when inoculated into AIDS patients, can destroy HIV-infected cells of the patient with high efficiency.

Mr. Stokes: How much is included in the FY 1995 budget request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Fauci: The NIAID included $32,553,000 in the FY 1995 budget request for gene therapy. The NIAID invested $28,282,000 in FY 1993, and FY 1994 expenditures in gene therapy are estimated to be $31,268,000.

PARTICIPATION OF MINORITIES IN BIOMEDICAL RESEARCH

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of historically black colleges and universities in biomedical research?

Dr. Fauci: A major NIAID initiative for Historically Black Colleges and Universities (HBCU) was an award to the Association of Minority Health Professional Schools (AMHPS). The AMHPS is a collaboration of eight HBCUs, which received a five-year grant in 1990 to increase the participation of faculty, staff, and students in basic and clinical research on HIV infection and AIDS.

In FY 1990 NIAID funded the AIDS Minority Infrastructure Awards, which were three-year awards made to three minority institutions, of which one was a HBCU, to enable them to develop the capability, expertise, and experience in conducting AIDS clinical trials. In FY 1993 NIAID issued a solicitation for AIDS Clinical Trial Units in minority institutions. In response to this competitive solicitation, four minority institutions, including two HBCUs (Howard University and Meharry Medical College), received four-year awards as AIDS Clinical Trials Units.

The NIAID has major commitments to several other programs for minority institutions and minority investigators, including those at HBCUs. Included are the Minority Biomedical Research Support program (15 awards; 6 to HBCUs), the Minority Access to Research Careers program (4 awards; 1 to HBCUs), and the Research Centers in Minority Institutions program (7 awards; 1 to HBCUs).

STAFFING LEVELS

Mr. Stokes: How many GS-15 and above positions are there in your Institute?

Dr. Fauci: The NIAID has 112 positions in the GS-15 and above categories.

Mr. Stokes: How many employees in your Institute are in GS-15 and above positions?

Dr. Fauci: The NIAID has 112 employees in the GS-15 and above categories.

Mr. Stokes: In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they?

Dr. Fauci: We currently have two GS-15 positions occupied by male African Americans. One is the Director of the Office of Research on Minority and Women's Health, and the other is the Deputy Director of the Division of Allergy, Immunology, and Transplantation.

Mr. Stokes: In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Fauci: In NIAID, we have no African Americans on appointments or awaiting promotion at the Grade 15 and above level among the cases pending for exception to the freeze.

Mr. Stokes: Has the NIH requested relief from the freeze, if so, what was the response?

Dr. Fauci: The NIH requested relief from the Public Health Service's (PHS) hiring freeze imposed in December 1993 because NIH had successfully managed its FTE ceiling. The request is under consideration by the PHS.

Mr. Stokes: If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Fauci: The NIAID does not have an EEO problem as a result of the freeze on hiring and the targeted reductions to positions in grades GS-14 and above, but our various recruitment efforts to further diversify the Institute workforce have been constrained. A lifting of the freeze would certainly have an impact on our efforts to enhance the diversity of our Institute's managerial workforce in terms of minorities--especially African Americans and Hispanics--and in meeting the racial diversity enhancement goals for identified position series that are contained in the recently expanded NIH recruitment and hiring program.

DISEASE PREVENTION

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Fauci: We have several significant vaccine development initiatives underway in our Institute. Through the Children's Vaccine Initiative (CVI), NIAID has joined a global initiative to develop new and improved children's vaccines that are safer, more effective, cheaper, and easier to administer.
CVI is an international effort to ultimately develop a single, heat stable, oral vaccine that will provide lifelong immunity to the major infectious diseases of childhood. NIAID's contribution to this goal includes research on new and improved vaccines that will protect against specific priority diseases and are potentially applicable for use in universal childhood immunization programs. Efforts in this area include the following:

- The need for improved immunization against rubella has been demonstrated by recent outbreaks of rubella and measles in the United States as well as a report by the Institute of Medicine (IOM) on the adverse effects of the existing rubella vaccine. The report cited evidence that receipt of the RA 27/3 rubella vaccine is causally associated with acute arthritis as well as limited evidence that it is associated with chronic arthritis. NIAID-supported researchers made significant progress toward an improved vaccine by developing a DNA clone of the rubella virus. This advance will provide the tools to develop a new engineered recombinant vaccine which will not cause arthritis;

- Immunization programs using the two forms of polio vaccines currently licensed in the United States have been highly effective and may soon lead to eradication of paralytic polio. However, concerns about reversion to neurovirulence and vaccine delivery problems, such as the need for continuous refrigeration, have prompted NIAID research efforts to attempt to improve and create safer polio vaccines. NIAID-supported researchers have developed a transgenic mouse model that is susceptible to the human poliovirus and can develop paralytic disease. This model is being used to understand the pathogenesis of the polio vaccine's neurovirulence, which is an important step in the potential development of a safer vaccine; and

- NIAID is supporting a major initiative to develop a vaccine to protect newborn infants against group B streptococcal (GBS) infections, the most common cause of sickness and death related to neonatal infection in this country. Immunization of infants is impractical for the prevention of GBS disease because most infections occur shortly after birth. However, immunization of women to stimulate maternal antibodies to protect the newborn is an alternative approach. NIAID is supporting the development of GBS glycoconjugate vaccines for immunizing pregnant women. A type III conjugated to tetanus toxoid vaccine is currently being evaluated in Phase I clinical trials. Additional GBS vaccines will be tested for safety and immunogenicity as they become available.

The development of an HIV vaccine is another priority initiative of the Institute. But before candidate HIV vaccines can be tested in humans, a large number of questions must be answered in animal models. One barrier to this effort is the fact that HIV will cause disease only in humans. Therefore, researchers have examined in animals other virus-induced immunodeficiency diseases that are similar to HIV infection in humans. One of the more useful animal models involves macaque monkeys infected with simian immunodeficiency virus (SIV), which duplicates many aspects of HIV in humans. Studies with the macaque monkey model showed that animals that had been successfully vaccinated against one strain of SIV using a whole, inactivated SIV vaccine also were protected against a second strain of the virus. This result is significant because it indicates that the variation seen in immunodeficiency viruses may not be as formidable an obstacle to HIV vaccine development as was once feared.

While preclinical studies continue to optimize strategies for HIV vaccine development, human trials of experimental HIV vaccines have been underway since 1987. The NIAID's Vaccine Evaluation Units are evaluating seven different HIV vaccines that are composed of the envelope proteins gp120 or gp160 found on the outer coat of the virus. These studies are evaluating the safety of the vaccines, determining whether the vaccines induce strong immune responses, and comparing responses to different doses of each vaccine. At this time, there are not sufficient data on any particular candidate vaccine to support an efficacy trial. However, several HIV vaccine approaches may produce such data within one to two years. Because of this possibility, NIAID is continuing to establish the necessary infrastructure for efficacy trials both domestically and internationally.

After decades of steady decline, the incidence of tuberculosis (TB) has begun to rise in the United States. Current diagnostic tests to identify infected patients and to determine which drugs can be used for treatment take several weeks before results are available, during which time the patient may be receiving drugs that are not effective and may transmit disease to others. Two NIAID-supported investigators have developed techniques for rapidly identifying TB and determining the drug susceptibility of TB isolates. The first assay is based on polymerase chain reaction (PCR) technology. PCR enables the amplification of very small amounts of DNA. The researcher identified a fragment of TB DNA, known as IS6110, that is unique to *M. tuberculosis* and then developed a PCR method to assay TB directly from clinical specimens, such as a sputum sample. The other assay uses luciferase, an enzyme that is part of the system that makes fireflies glow. The investigator constructed a mycobacteriophage (a bacterial virus specific for the TB microorganism) that contains the gene to produce luciferase and can be used to insert the luciferase gene into the TB bacterium. In the assay, the phage and luciferin are added to TB organisms from a patient specimen and an anti-TB drug. Using the investigator's system, light production would normally be seen within 15 minutes. However, if the organism is grown in the presence of an effective antibiotic, it will be killed and there will be no light production. Not only is this a rapid and sensitive method for detecting resistant strains, but because of its potential for automation, large numbers of samples could be precessed in a short time. This assay can also be used for screening large numbers of potential anti-TB drugs.

Asthma is a major medical problem in this country--it affects some 10 million people, more than one-third of whom are under age 18. Recent studies indicate that African Americans and Hispanics living in inner-city areas may have unusually high rates of asthma morbidity and mortality. Asthma morbidity and mortality are known to be a function of many factors, such as the patient's physiology, environmental exposure to allergens, and access to medical care, as well as the quality of that care. However, it is not known to what degree these factors account for the significant differences in morbidity and mortality and whether other, unique factors contribute to the high rates of morbidity and mortality among Blacks and Hispanics living in the inner city. To address the increasingly serious problem of asthma in minority children living in urban areas, the NIAID has funded eight groups from seven cities throughout the United States to conduct the National Cooperative Inner City Asthma Study. The first phase of this study will identify factors, particularly behavioral factors, that are contributing to alarming increases in morbidity and mortality from asthma among minority children in inner cities. In the second phase, the identified factors will form the basis of a multicenter clinical trial to develop and evaluate behavioral and social approaches to reducing these rising asthma rates.

Another program sponsored by the NIAID to reduce asthma morbidity and mortality among Blacks and other minority groups involves the Asthma Education Program for Hospitalized Inner-City Children, which is funded under the Institute's Centers for Interdisciplinary Research on Immunologic Diseases. The study tested a self-management education program designed to help hospitalized asthmatic children control acute episodes of their disease. The study found that the education program increased the children's knowledge of the early warning signs of acute asthma, their sense of personal control, and their use of self-management techniques for acute asthma episodes. The program also decreased the children's use of emergency hospital services. In addition, the NIAID's Asthma and Allergic Disease Cooperative Research Centers, as well as its Immunologic Disease Cooperative Research Centers, are exploring ways to reduce the severity and incidence of asthma in minority populations through outreach, demonstration, and education programs in inner cities.

RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising basic research opportunities at your Institute? Elaborate on the benefits to be achieved from further investments in this research.

Dr. Fauci: NIAID has several exciting and promising basic research opportunities currently being exploited by its extramural and intramural programs. The following are examples of some of these projects:

HIV/AIDS RESEARCH

Polymerase Chain Reaction (PCR)

NIAID-supported investigators independently observed that during early stage HIV infection and clinical latency there are higher viral burdens in lymph nodes than in peripheral blood. The same conclusions were reached using *in situ* hybridization to visualize gene sequences in histological sections. HIV was trapped on the follicular dendritic cells of lymph nodes. These results demonstrate that HIV disease is active in the lymphoid tissue throughout the period of clinical latency, and measurements of infected cells in the peripheral blood may be misleading in determining viral load. Further, the accumulation of infectious virus in lymph nodes may provide a site for transmission of HIV to non-infected immune cells as they pass through the node.

The utilization of Quantitative Competitive Polymerase Chain Reaction (QC-PCR) has demonstrated that significant levels of virus are present during all stages of HIV infection, including the asymptomatic phase. Quantification of HIV in plasma by QC-PCR provided a new, direct virologic end-point for monitoring virtually all infected patients and may be of particular utility in assessing antiviral efficacy in clinical studies, especially in early stage disease where conventional virologic markers are often negative.

Development of a rapid and economical acid-dissociated HIV p24 antigen detection of HIV p24 antigen ELISA assay (ICD p24 Ag) that disrupts immune complexes to permit the detection of HIV p24 antigen in cord-blood and serum samples from neonates, thereby facilitating the serologic detection of HIV infection. This research is leading to improvements in diagnosis of potentially HIV-infected children.

Using samples from patients with acute HIV infection, genotypic and phenotypic characteristics of the virus that was successfully transmitted were studied. The viral population found in the seroconverters was genotypically homogenous. When compared with the sequences found in the blood of the sexual partner (transmitter), the transmitted virus represented only a minor variant. In addition, phenotype studies showed that the transmitted viruses have uniform biological properties *in vitro*. Specifically, they were macrophage tropic but not T-cell tropic. These features of the transmitted viruses have important implications for vaccine development.

ALLERGY, IMMUNOLOGY AND TRANSPLANTATION

The Use of Cytokines to Regulate Immune Responses

Cytokines, which are small protein molecules, orchestrate immune responses and play important roles in the pathogenesis of infectious, inflammatory, allergic, autoimmune, and malignant diseases. The NIAID supports a wide variety of research concerned with: (1) the structure and physiological functions of cytokines and their receptors; (2) the roles played by cytokines in the control of immune responses; (3) aberrations in cytokine function that results in disease; and (4) the use of cytokines in immunotherapy and prophylaxis of disease. A recently discovered cytokine, interleukin-12 (IL-12), has received considerable attention from NIAID-supported investigators. IL-12 appears to play a critical role in immunity to infectious microorganisms, especially those that thrive inside the cells of the infected host (e.g., certain bacteria and protozoan parasites). Treatment of laboratory animals with IL-12 promotes elimination of these intracellular infections. As a result of both directing the path and magnitude of an immune response, IL-12 can function as a potent immunological adjuvant. A variety of investigations are in progress, many supported by the NIAID, to explore the potential of IL-12 to enhance immune responses to weak microbial and tumor antigens and in boosting the meager immune responses in infants and the elderly. There is a strong possibility that IL-12 may be useful in the process of vaccinating humans against infectious diseases such as tuberculosis and leishmaniasis.

Antigenized Antibodies as Vaccines

The strategy behind this method of vaccination is to increase substantially the efficiency with which antigens, such as those of pathogenic microorganisms, stimulate the immune system. The procedures involve chemical coupling of the antigens to certain other molecules, called carriers, that stimulate vigorous immune responses. The passenger antigens, riding piggy-back on the carrier molecules, may then elicit strong, protective immunity. Among the proteins that function as good carrier molecules are immunoglobulins (i.e., other antibodies) because they are efficiently ingested by key cells, called antigen presenting cells (APCs), that are required to initiate immune responses. The complex of antigen attached to the immunoglobulin is referred to as an "antigenized antibody." Once the antigen is escorted by the carrier antibody into the APC, the antigen is likely to be quite proficient in triggering an immune response and inducing a state of long-lasting, protective immunity. Pre-clinical studies supported by the NIAID have revealed that this approach works well in inducing protective immunity against the influenza virus in animal models.

Inducing Tolerance with Donor Immune Tissue

It has been demonstrated, in a rhesus monkey model, that about one-third of the animals treated with an infusion of donor bone marrow and anti-thymocyte antibody have enhanced survival of a kidney transplanted from the same donor. It has been shown that the immunosuppression normally required to prevent graft rejection may be discontinued in these animals without any adverse effects, that the immunologic non-responsiveness is specific for the bone marrow donor, and that the non-responsiveness correlates with development of donor bone marrow cells in the recipient's tissues. This non-responsiveness is achieved through a subpopulation of donor bone marrow cells which neutralize the recipient effector cells involved in the organ rejection process. This work has enormous implications for human transplantation because it suggests a means of eliminating the need for transplant patients to receive lifetime immunosuppression, which carries with it the significant increased risk of infection and malignancy as well as other side effects.

Use of Stem Cells to Treat and Cure Chronic Infection

Hematopoietic stem cells (HSC) have the function of generating the various types of cells found in normal blood and lymphoid tissues. All of the mature cells of the immune system originate from HSC, as do both the red and white blood cells. Therefore, the ideal therapeutic approach to treating diseases that arise from either a congenital deficiency of mature blood cells (e.g., anemias or immunodeficiencies) or from destruction of blood cells (e.g., from toxins, irradiation, tumors, HIV infection) is the replacement of HSC. Because HSC are especially abundant in normal bone marrow, the classical approach has been bone marrow cell therapy. This creates an exceedingly complex problem, complicated in part by the fact that most of the cells present in bone marrow are not HSC. Consequently, there is a need to be able to isolate, cultivate and manipulate HSC and, although these are extraordinarily difficult problems, progress has been impressive. Parallel studies have been conducted with mouse and human bone marrow; mouse marrow is an excellent model of human marrow. It is now possible to isolate human HSC in highly enriched form on a limited scale, and methods for increasing the yield are at hand. It has been established that only a small number of HSC are required to completely restore all of the normal blood cells in a human recipient. One of the remarkable advances has been the discovery that allogeneic (i.e., genetically dissimilar) HSC can be introduced into a recipient without the complications of severe graft-versus-host immune reactions. This greatly simplifies the potential use of marrow from genetically non-identical donors. The isolation of HSC in highly enriched condition has paved the way for studies on the transfer and expression of genes within the HSC. The introduction of such stem cells carrying therapeutic genes to correct deficiencies or treat specific disorders in recipient humans is the most appealing approach to gene therapy. Ultimately, HSC will be used extensively for both therapeutic and prophylactic purposes. It is critical that research concerned with the properties and uses of HSC continue on a broad front.

MICROBIOLOGY AND INFECTIOUS DISEASES

Group B Streptococcus (GBS)

Five different serotypes of GBS are pathogenic and cause sepsis, meningitis and pneumonia in newborn infants. Infants acquire the infection from their mothers during delivery, and in order to prevent this devastating infection we need a multivalent vaccine, with each of the five different capsular polysaccharides carrying a protein carrier load. Recently, 90 percent of non-type III strains were discovered to have an alpha protein that could possibly serve as the carrier protein for a type III polysaccharide and essentially provide protection against all GBS strains. An NIAID researcher has cloned the gene and sequenced the protein. The next essential step to be supported is the conjugation of the alpha protein to type III polysaccharide to form a true combination vaccine.

Autoimmune Diseases in Women

Women are more susceptible to autoimmune diseases than men. Although the mechanisms are not well understood, cytokines are likely to play a critical role because they affect immune cell function and proliferation. NIAID grantees have found striking differences in the secretion of the cytokine interleukin-1 in women compared with men and in women at different times during the menstrual cycle. A more comprehensive picture of gender-related differences in the immune system should lead to a better understanding of immunologically mediated disease in general and in particular of diseases that occur more often in one sex or the other. Improved understanding will point the way to new approaches to prevention and treatment.

Viral Pathogenesis

Increased understanding of the intricacies of viral pathogenesis should allow for the development of viral vaccines and antiviral therapies. Viruses have developed a number of strategies to avoid or subvert the host immune system. These range from preventing transport of MHC I antigens to the host surface (adenoviruses), to blocking the conversion of IL-1 from its inactive to active form (poxviruses), to carrying an IL-10 gene (Epstein-Barr Virus [EBV]). Many of these genes have been identified as "by-products" of other studies. Understanding the function of them in disease pathogenesis is especially important for both live-attenuated vaccines and subunit vaccines where the viral protein interacts with immune molecules, e.g., EBV gp350 binds to the CR2 surface protein whose biologic function is as the C3b receptor. These immunomodulatory viral proteins also have potential as antagonists of host molecules and thus may have therapeutic value. Finally, if viral genes or genomes are used as therapeutic vectors, the presence or absence of these genes could impact on vector function.

Immune Response and Regulation

Increased knowledge of the immune response and its regulation should allow for the development of improved vaccines and immunotherapies. Advances in immunology research have demonstrated the complexity of the immune response and the importance of the route by which an individual is exposed to an agent as well as the role of host genetic factors in determining whether an individual is infected, makes a protective response or makes an immunopathological response. The recent availability of reagents to measure the different cell types, cytokines, and lymphokines involved in a response combined with the ability to use molecular biological and recombinant DNA technologies to prepare components of infectious agents should allow for rapid progress in this area.

Mechanisms of Resistance to *Pseudomonas areuginosa*

This area of research involves the study of the mechanisms by which the pathogenic bacterium causes diseases in cystic fibrosis (CF) patients. It includes the role of virulence factors in the pathogenesis of the disease, the involvement of environmental factors in the establishment of infections, and the pathologic conditions, imposed by the organism, that alter host defenses. CF is a genetic disease of the white population that has a frequency of 1 in 25. There is usually significant morbidity and mortality associated with the disease due mainly to lung damage. Recently, there has been considerable interest in the idea that one can "cure" the disease by correcting the basic genetic defect at the level of the DNA - an approach called gene therapy. However, in spite of this new advance, it is still necessary to conduct basic research in an effort to understand how the immune system responds to the large number of virulence factors and how immunoprotective measures can be attained.

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Fauci: In general, the scientists that are coming out of the pipeline are trained in the use of the latest technologies and are capable of developing the advanced technologies for tomorrow. In general, there are adequate numbers of investigators trained in the areas that address NIAID's scientific mission, both in terms of pre- and postdoctoral trainees. However, two areas that are within the NIAID scientific agenda require additional researchers: AIDS and tuberculosis.

VACCINE DEVELOPMENT

Mr. Stokes: To what extent is the Institute involved in the new and exciting initiatives underway in vaccine development that would allow patients to be immunized against their own tumor? How much closer are we to having an AIDS vaccine?

Dr. Fauci: The National Cancer Institute has the lead for vaccines that would allow patients to be immunized against their own tumor. The NIAID vaccine program does support research on infectious diseases that themselves create risks for tumors. An excellent example is hepatitis B infection, which is a risk factor for hepatocellular carcinoma. NIAID's Intramural and Extramural Research Programs have supported research studies which have resulted in a safe and effective vaccine now used within the universal immunization regimen of children in the United States. NIAID also supports research on human papilloma virus, which is causally associated with cervical cancer in women.

CLINICAL TRIALS

Mr. Stokes: How much is included in the FY 1995 Budget Request for clinical trials?

Dr. Fauci: The NIAID included $256,384,000 in the FY 1995 budget request for Clinical Trials.

Mr. Stokes: How does this amount compare with the amount invested in clinical trials in FY 1994 and FY 1993?

Dr. Fauci: The NIAID invested $228,251,000 in FY 1993, and FY 1994 expenditures in Clinical Trials are estimated to be $247,344,000.

Mr. Stokes: Would you please comment on the economic benefits and the quality of life benefits of some of the major clinical trials supported by your Institute?

Dr. Fauci: We have done exceptionally well in realizing economic and quality of life benefits as a result of the clinical trials conducted by our Institute. The following represent benefits accrued from our most recent major clinical trials:

National Cooperative Inner-City Asthma Study

Asthma morbidity and mortality have been increasing in the United States for the last decade. This increase has been concentrated disproportionately among minorities and children. The National Cooperative Inner-City Asthma Study (NCICAS) is an eight-site study designed to develop effective interventions to reduce asthma morbidity and mortality among minority children, ages four to nine, residing in the inner-city. The products from NCICAS and future work on different age groups offers great potential for cost savings.

Although asthma is a disease with low mortality, its economic costs are enormous with an estimated cost in the United States of $6.2 billion for all age groups in 1990, the last year for which cost estimates and asthma morbidity and mortality data are available. Despite the widespread assumption that asthma is a mild illness, a significant proportion of the 1990 costs were due to hospitalizations and emergency room visits. In addition, 1990 costs for outpatient visits and medications are estimated at over $1.6 billion. Asthma leads the list of childhood diseases causing school absenteeism; the largest single indirect cost of asthma in 1990 was $1 billion for decreased productivity due to loss of work/school days.

Interventions being developed as part of NCICAS are estimated to reduce significantly the frequency of hospitalizations and the use of emergency rooms through increased use of less costly outpatient visits and the appropriate use of asthma medications. The total potential cost savings in the United States from these interventions is estimated at approximately $560 million annually for all age groups as displayed in the following table:

Cost Area	1990 Pre-Intervention Costs	Estimated Effect of the NCICAS Intervention	1990 Post-Intervention Costs	Net Difference
Hospitalization	$1,700,000,000	66% Reduction	$560,000,000	-$1,140,000,000
Emergency Room Visits	$295,000,000	50% Reduction	$147,000,000	-$147,000,000
Outpatient Visits	$537,000,000	33% Reduction	$715,000,000	+$178,000,000
Medications	$1,100,000,000	50% Reduction	$1,650,000,000	+$550,000,000
Total Estimated Savings				+$560,000,000

Cooperative Clinical Trial in Kidney Transplantation

Kidney transplantation provides the best quality of life and, when successful, is the most cost effective treatment for end-stage renal disease. More than 80 percent of transplant recipients report that they are physically active, and most patients compare favorably with the general population in terms of quality of life satisfaction and well-being. However, patients with a failed transplant have a poorer quality of life than patients on dialysis. Rejection is the major cause of transplant failure and occurs when the recipient's immune system recognizes the transplanted organ as foreign and attempts to remove or destroy the invader. As a result, transplant recipients are on a lifetime regimen of immunosuppressants, drugs that suppress the immune response. However, generalized immunosuppression has very serious side effects, including increased rates of infection and of very aggressive cancers. Therefore, a delicate balance must be maintained between adequate immunosuppression to prevent rejection without causing harmful side effects. Often, this balance is not achieved. NIAID is supporting research on this approach using animal models with great success. One study has used monkeys with transplanted kidneys that have survived for over two years without any immunosuppression. The real challenge is to achieve these results in humans, and to this end, the NIAID is supporting the Cooperative Clinical Trial in Kidney Transplantation. The eight centers participating in this cooperative clinical trial group are investigating new, innovative treatment modalities to enhance transplanted kidney survival. Developing effective treatments through this project can greatly enhance the quality of life of transplant recipients and achieve a major cost savings.

Generalized immunosuppression costs approximately $6,000 per year for each transplant recipient and is normally required for the remainder of the recipient's life. Given that there are over 9,000 kidney transplants performed each year, the savings in immunosuppressive medication costs alone would be $54 million annually. This does not take into account the added costs of rejection episodes, which usually require hospitalization and treatment, or the significant costs associated with treatment of infection and aggressive (and most often fatal) lymphoma as predominant side effects of generalized immunosuppression.

A specific example of costs savings in this area pertains to NIAID support for the development and testing of a new anti-rejection therapy antibody. This antibody, called T10B9, significantly increases the chances that a transplant will be saved with far fewer side effects from this treatment compared to the current standard of practice antibody used. The fewer side effects means that this agent can be administered on an outpatient basis, versus the current rejection treatment that has to be administered in the hospital and has significant serious side effects associated with its use. It is estimated that use of this new agent could result in savings of between $38 million and $58 million annually.

Herpes Simplex Encephalitis (HSE)

HSE, which affects from 250,000 to 500,000 persons per year, is the most common cause of sporadic fatal encephalitis in the world. In the absence of effective therapy, mortality is in excess of 70 percent and only 2.5 percent of patients overall return to normal function following disease. The NIAID-supported Collaborative Antiviral Study Group's (CASG) investigators were among the first to utilize brain biopsy as a uniform diagnostic approach in HSE. This resulted in clarification of the presentation, diagnosis and outcome of patients with HSE. Consequently, therapies for HSE markedly improved following these advances. The CASG demonstrated that vidarabine therapy decreased mortality overall from 70 percent to 28 percent one month after disease onset and 44 percent six months later in biopsy-proven disease. The CASG later showed that acyclovir was more efficacious than vidarabine--decreasing mortality to 19 percent six months post treatment--and is better tolerated in HSE patients. Currently, acyclovir is the treatment of choice for HSE. Acyclovir improves both mortality and morbidity, but the outcome remains poor particularly in high risk individuals.

Neonatal Herpes Simplex Virus (HSV)

A recent clinical trial evaluated therapy against neonatal HSV infections. HSV infection in newborn children is usually acquired from contact with infected maternal genital secretions. Approximately 1,500 children are diagnosed with neonatal herpes each year in the United States. In the absence of therapy, HSV infections can be life-threatening and invariably associated with increased risk of severe neurologic impairment. It is estimated that nearly $300 million dollars is spent annually for the care of children with neonatal HSV infections. The CASG demonstrated that acyclovir is equally as effective as vidarabine for the treatment of neonatal HSV infections. When the HSV infection was localized to the skin, eye and mouth, 90 percent and 98 percent of children treated with vidarabine and acyclovir, respectively, were developing normally two years later. Following the development of encephalitis, 50 percent of survivors treated with vidarabine and 43 percent of survivors treated with acyclovir were developing normally. Infants who had survived disseminated infection showed a normal development rate of 62 percent and 57 percent, respectively, following vidarabine and acyclovir therapy. The safety and tolerance of acyclovir prompts its recommendation as the treatment of choice for this disease. The CASG is presently conducting a clinical study to further evaluate high-dose acyclovir for the treatment of neonatal herpes virus infections. Patients will be evaluated during the acute phase of therapy for improved mortality and morbidity. Neurological development, sensorineural function and developmental psychologic assessments will be performed at 6, 12, 24, 36, and 48 months after therapy. These evaluations will directly address quality of life issues, such as school attendance and performance, and level of parental or institutional care required.

Pertussis

The NIAID supports two large-scale field trials of new acellular pertussis vaccines, which are expected to provide excellent protection against whooping cough and cause far fewer adverse reactions than the current whole cell pertussis vaccines. The economic benefits of doing efficacy trials with new and/or improved vaccines are many. The availability of a vaccine which is shown to be efficacious reduces both the morbidity and mortality caused by the organism for which the vaccine is designed to protect against. Immunization is still considered the cornerstone for building a primary care system for all. In areas where medical care and basic sanitation are largely unavailable, and malnutrition and childhood infections are rampant, immunizations with proven vaccines may represent the most cost-effective approach for increasing child survival. UNICEF estimates that current immunization programs save the lives of more than 3.2 million children annually. Other estimates indicate that the full utilization of existing vaccines could save an additional 1.7 million children each year. The availability of new and improved vaccines against diarrhea, malaria, respiratory diseases, and meningitis might also prevent another five to six million deaths.

Effective vaccines can also save dollars as well as lives. In addition to the enormous medical costs associated with the treatment of individuals suffering from various infectious diseases, there are also other costs which add to the burden of disease and thus, must also be considered. This would include such factors as the loss of work by affected parents who must care for ailing children, loss of future productivity for those suffering from chronic disabilities, complications leading to special care and/or the use of sophisticated medical equipment, and illnesses due to disease which lead to major limitations of normal activity or function (e.g., reproductive impairment leading to infertility). Finally, a successful vaccine program, which ultimately leads to the eradication of disease such as the case with smallpox, can reduce health dollars devoted to immunization and surveillance programs.

HIV/AIDS Research

The recent demonstration from a NIAID-sponsored trial of a 67 percent reduction in the transmission of HIV from pregnant women to their infants when the woman receives AZT during the pregnancy and the infant is treated for the first six weeks of life. These dramatic findings could lead to significant reductions in the numbers of new cases of HIV in children.

In the United States, the cost of treating all persons with HIV infection is expected to increase 48 percent from $10.3 billion in 1992 to $15.2 billion in 1995. Most of this expense is associated with hospitalizations to treat the opportunistic infectious associated with HIV disease. NIAID-sponsored clinical trials have defined the standard of care for acute treatment and prophylaxis of *Pneumocystic carinii* pneumonia.

These findings, if widely used by practicing physicians, could have an impact on both the quality of life and cost of care of individuals with AIDS.

Mr. Stokes: To what extent has the Institute increased the number of minorities participating in its clinical trials? What progress is being made?

Dr. Fauci: NIAID has been at the forefront of recruiting minorities into its various clinical trial programs. Within its AIDS Clinical Trials Network, the percent of minorities participating in these trials in 1993, 43.7 percent, nearly mirrors the percent of AIDS cases in minority populations in the United States, 49 percent. We have also added four AIDS clinical trial units, housed in minority institutions, to our AIDS Clinical Trials Network.

NIAID is currently conducting a National Cooperative Inner City Asthma Study which is studying asthma in African Americans and Hispanics for the purpose of developing low-cost interventions. NIAID is also collaborating with the Centers for Disease Control and Prevention in a study of AIDS transmission in women entitled "The Women's Interagency Health Study."

In a recent collaboration with the Office of Research on Minority Health, the NIAID has initiated a study of HLA genes focusing on Hispanics to improve organ transplantation tissue matches in this population. This study is built on studies previously conducted in African Americans and Native Americans. In addition to these ongoing efforts, NIAID plans to fully implement the new guidelines for inclusion of women and minorities in clinical research, including clinical trials.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Fauci: NIAID has participated in the Research Supplements for Underrepresented Minorities (RSUM) program since 1989, when NIH initiated the program. The RSUM program is designed to provide support for minority scientists who are interested in working with a Principal Investigator of an NIAID grant. This program provides support for high school, undergraduate, medical and graduate students, as well as postdoctoral and other senior scientists. NIAID's portfolio of minority supplements is mostly concentrated on support of graduate students working on their Ph.D.s and postdoctoral scientists. Although the program has only been in existence for five years, three of our postdoctoral awardees have successfully competed for an individual research grant. The number of graduate students who have been successful in obtaining an independent research grant is not available, but it should be kept in mind that the scientific career of these individuals is still in their formative years. It generally takes a graduate student five years to complete his or her Ph.D., plus an additional three to five years of postdoctoral work to become competitive for an individual research grant. The NIAID is pleased at the number of successful RSUM postdoctoral minority scientists, but would like to see the pool increase. To this purpose, NIAID has begun a program to provide minority graduate and postdoctoral scientists with a special mentoring program entitled "Bridging the Career Gap."

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Fauci: Research in biotechnology affects virtually all of the research presently underway at the NIAID and is sure to remain vitally important in future studies. For example, there is a wide variety of diseases that originate from the transmission of aberrant genes from parent to offspring. The frequency of any one of the diseases in the human population is low, but in aggregate these genetic diseases constitute a major health problem. The most distressing fact about these genetic diseases is that many of them are not fatal *in utero* but have devastating effects on the afflicted individual. Methods of treating these diseases remain primitive and, at best, treat the symptoms but not the underlying disease. At present, the great hope for dealing with genetic diseases lies in genetic therapy, i.e., the addition of a "good" gene to counteract an aberrant homologue under conditions that will allow controlled expression of the normal gene.

The objectives of research concerned with gene transfer during the next few years, perhaps the next decade, must be to solve questions such as:

- What type(s) of cells are most suitable as recipients of transferred genes from two perspectives, (i) efficient uptake, integration and expression of exogenous genes, and (ii) patient acceptance of the cells and long-term stability and survival of the cells once introduced into patients;

- How to modify genes, by adding or subtracting segments of DNA (i.e., preparing gene "constructs"), so that the genes have a high probability of being integrated at the appropriate sites in the host cell genome where they will be subject to normal, host regulatory elements. At present, these problems are particularly relevant to the development of animal models of disease; and

- How to modify and manipulate genes so that they may be introduced directly into patients, targeted to the cells in which they normally are expressed, and ensure that they are both taken up by those cells and properly integrated into the genome of those cells. This is the ultimate goal of research dealing with gene therapy.

One of the primary goals of the NIAID is to develop a coordinated approach to further the conquest of vaccine-preventable diseases. Opportunities are burgeoning for the development of new and improved vaccines for the entire spectrum of infectious agents--bacteria, viruses, fungi, and parasites. Recombinant DNA technology, the production of monoclonal antibodies by hybridomas, nucleic acid sequencing, and peptide synthesis have opened the way for producing refined or synthetic highly specific immunogenic antigens that can be incorporated into vaccines. These advances, coupled with the possibilities for manipulation of antibody and cellular immune responses, offer hope for prevention, and ultimately eradication, of many diseases.

The Institute of Medicine's Committee on Emerging Microbial Threats to Health recently reported that the threat posed by disease-causing microbes may be expected to continue and even intensify in coming years. Some emerging diseases result from selection of new genetic strains and variants. Microorganisms such as viruses and bacteria have relatively few genes and small amounts of nucleic acid. One mutation could result in an enormous change in the ability of the organism to infect, cause severe disease, and/or spread in epidemic proportion. This relatively rapid evolution also is a product of their vast numbers, very rapid replication rate, and inherent genetic instability. This evolutionary advantage on the part of microorganisms is often seen as the cause of re-emergence of diseases that had previously been controlled by antibiotics and other drugs (e.g., drug-resistant TB and malaria). Clearly, biotechnology research will be an instrumental component of research directed towards the development of new therapeutic and vaccine strategies for the control of new and reemerging microbes.

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Fauci: In FY 1993 NIAID awarded $12,967,000 to minority institutions in support of biomedical research and training.

Mr. Stokes: Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Institute's programs and activities.

Dr. Fauci: Several programs for minority institutions, to which NIAID has a major commitment, are designed specifically to support the development of the necessary infrastructure so that such institutions would be able to compete more successfully for research awards. A good example is the Research Centers in Minority Institutions (RCMI) program, which is administered by the National Center for Research Resources (NCRR). Awards have been made to 18 minority institutions for the purpose of developing a competitive basic research environment that would attract highly qualified faculty in very specialized areas such as molecular biology, neurosciences, renal physiology, retrovirology (including HIV), pharmacology, immunogenetics and neonatology. In FY 1993 NIAID provided approximately 2.3 million dollars to support seven such awards.

Two initiatives, unique to NIAID, also foster support for the appropriate basic and clinical research infrastructure. The five-year Association of Minority Health Professional Schools award, made in 1990 to eight Historically Black Colleges and Universities (HBCU), was designed specifically to assist faculty and staff at those institutions in becoming more successful in the competition for HIV/AIDS research awards. The other initiative was the Minority Infrastructure Initiative launched in FY 1990, with awards made to three minority institutions, including one HBCU. These awards were to support the development of the appropriate clinical trials infrastructure so that the institutions would be more competitive for AIDS clinical trials awards. This program was an unqualified success in that four minority institutions, including two HBCUs, later competed successfully in FY 1993 for AIDS clinical trials awards.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research and research training.

Dr. Fauci: We have several programs that are targeted to increasing the participation of underrepresented minorities in biomedical research and research training. The following describes the various programs that we support at each rung of the academic ladder:

Adopt-A-School Program

The NIAID has "adopted" a local area high school as a means of addressing the growing concern about the lack of minority participation in the biomedical sciences. The Institute felt that it should become more involved with schools closer to home by adopting a local high school with the goal of providing scientific enrichment for it students. In the Fall of 1991 the NIAID and Dunbar Senior High School, located in Washington, D.C., noted for its pre-engineering and science program curricula, agreed to enter into a formal partnership beginning that would focus on students in the engineering and science disciplines. The program has enabled NIAID and Dunbar High School officials to enter into a cooperative relationship that benefits both the school and the Institute. As part of this program, students are exposed to a scientific environment in which they can nurture their interest in the sciences. Students, teachers, and administrators alike are developing a better understanding of the importance of research and the role of NIH scientists and support staff.

The Introduction to Biomedical Research Program (IBRP)

The IBRP program is divided into two phases. Phase I is an affirmative action initiative and is designed to inform academically talented college juniors, graduating seniors, and first-year graduate or medical students from underrepresented minority groups about career opportunities in the broad field of biomedical research. This initiative grew out of the need to increase the number of minority scientific researchers in this country. This first phase consists of a series of scientific small group lectures, interviews, and a tour of the NIH Clinical Center and the National Library of Medicine. Students have the opportunity to discuss current research initiatives, scientific advances, and career concerns with our intramural scientists. The four-day conference is held annually in February at the Bethesda campus of NIH. NIAID provides resources for the entire program, including room, board, and airfare from their home institutions for the participating students. Fifty-nine students participated in Phase I in FY 1994.

Phase II of the program, or the NIAID Summer Program, is designed for college students in their junior year or graduating seniors planning to attend graduate or professional school in the fall. First-year graduate or medical school students with an interest in gaining actual work experience in the field of biomedical research also are sought for participation in this segment. Phase II is held from mid-May through September. Eligibility requirements are similar to Phase I, except that this program is not limited to minorities. However, annually between 45 and 55 percent of the selected students have been from minority or ethnic origin backgrounds. The program provides students with ten weeks of biomedical research training in one of NIAID's highly productive intramural research laboratories. Laboratories are located in Bethesda, Rockville, and Frederick, Maryland, and in Hamilton, Montana. The mentor system is used, and career counseling is offered. Attendance at research seminars is encouraged, and students often present their research projects to peers and specialists in their particular field of interest. In FY 1994 21 students were selected, of which 50 percent came from minority backgrounds.

Bridging the Career Gap for Underrepresented Minority Researchers

This program was developed to bring underrepresented minority investigators, currently funded by the NIAID under various training and research supplemental awards, to the NIH campus for a two-day seminar. The NIAID, with the collaboration of the NIH Office of Research on Minority Health, sponsored this new initiative. The purpose of this seminar is to allow for the exchange of science; to impart information on applying for research project grants; to acquaint the participants with the opportunities and options open to them in the field of biomedical research; and to provide an opportunity to meet with NIAID intramural and extramural staff for the purpose of establishing mentors. The program is also an attempt to let these young researchers know that the NIAID has a vested interest in their academic future through the establishment of a "bridging program". The first seminar was held in October 1993 and had 48 participants.

Research Supplements for Underrepresented Minorities (RSUM)

NIAID has participated in the RSUM program since 1989, when NIH initiated the program. The RSUM program is designed to provide support for minority scientists who are interested in working with a Principal Investigator of an NIAID grant. This program provides support for high school, undergraduate, medical and graduate students, as well as postdoctoral and other senior scientists. NIAID's portfolio of minority supplements is mostly concentrated on support of graduate students working on their Ph.D.s and postdoctoral scientists. Although the program has only been in existence for five years, three of our postdoctoral awardees have successfully competed for an individual research grant.

NIAID also supports the following NIH-wide minority training programs: Minority Biomedical Research Support (MBRS), Minority Access to Research Careers (MARC), Research Centers for Minority Institutions (RCMI).

Mr. Stokes: There has been a great deal of publicity on a possible racial bias in transplantation and in the organ allocation system--the system for deciding who receives a transplant from a particular donor. What is NIAID doing to address this issue? Is there scientific evidence that supports or refutes this?

Dr. Fauci: It is true that African Americans and women receive fewer transplants than would be expected from their representation on the waiting lists. However, there are sound scientific reasons for this. First, different segments of the population are genetically distinct. For example, blood types of African Americans contain different antigens when compared with the predominately white organ donor pool, causing problems in matching potential recipients with donor organs. Second, there is some evidence that certain racial groups may have a more "aggressive" immune system than do others, a factor that has been shown to contribute to the frequency and severity of organ rejection and to limit access to organs by disqualifying candidates from transplantation. Third, the distribution of multiple transplant antigens varies among different races and is less well-defined among racial minorities. This means that: (1) it is more difficult to identify truly matched donors; (2) it is not always possible to assess accurately the degree of match and mismatch; and (3) the effect of these antigens on susceptibility to end-stage organ disease and transplant survival is impossible to evaluate accurately.

These factors would make it more difficult for some potential transplant recipients to find a compatible donor and would also increase the likelihood of organ rejection. In support of this, a recent study by the Rand Corporation has shown that African Americans are presensitized to organ donors more frequently than are whites. Two major factors contribute to this increased level of presensitization among African Americans: (1) transfusion with blood mostly from white donors who have different transplantation antigens (which also occur in the blood); and (2) a higher percentage of women, who as a group have increased sensitization due to pregnancy, among African American patients. According to this report, these factors account for most or all of the disparity in transplantation rates between African Americans and whites. This finding was reported by one of the authors of the original Office of the Inspector General report which stated that African Americans waited for transplants 2.5 times longer than whites, and fully accounts for that waiting time disparity.

To address the medical issues surrounding organ transplantation in minorities and women, NIAID supports the following basic and clinical research projects:

- NIAID, in cooperation with the NIH Office of Research on Minority Health, is supporting a major study to improve the characterization of HLA antigens in African Americans, Native Americans, and Hispanics. These antigens are not only those used in matching donors with potential transplant recipients but also play a major role in susceptibility to many diseases that lead to the need for transplantation;

- NIAID funds multiple studies aimed at developing ways to render a recipient immunologically non-responsive to donors. This is particularly important to those with more aggressive immune systems or those who have been sensitized by blood transfusion, pregnancy, or a previous transplant; and

- NIAID provides substantial support for studies to characterize the mechanisms that lead to transplant rejection and, using this information, to design interventions to prevent rejection by controlling these processes. The NIAID's National Cooperative Clinical Trial in Kidney Transplantation represents a major effort in this area with African Americans comprising 47 percent of the current total of 175 study participants.

Many of the issues surrounding transplantation today are directly related to a resource shortage, i.e., an inadequate supply of donor organs to provide transplants to all those in need. To address that problem, the overall goal of the NIAID is to develop knowledge that will reduce the need for transplantation by finding ways to prevent and/or treat the diseases that lead to transplantation as the most effective and often only medical treatment. In addition, because one of every six patients awaiting transplantation has already received a transplant that failed, NIAID is supporting research directed toward ways to prevent and treat graft rejection--one of the leading causes of transplant failure.

HIV/AIDS RESEARCH

Mr. Hoyer: Dr. Fauci, in FY 1994 was the $227 million increase in AIDS research funding distributed among the 21 ICDs that conduct AIDS research based on scientific criteria and according to the priorities articulated in the strategic plan?

Dr. Fauci: The $227 million increase for FY 1994 that was distributed among the ICDs was based on the scientific priorities and scientific opportunities that exist in HIV-related research according to the NIH Five Year Plan for HIV-Related Research. The Plan sets forth prioritized objectives and strategies in the five basic scientific areas that currently categorizes AIDS research: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral research. The Five Year Plan was developed by the Office of AIDS Research and cleared by the Department and the Office of Management and Budget on June 30, 1993, and signed into effect on September 1, 1993, and forwarded to Congress.

Mr. Hoyer: Dr. Fauci, in the FY 1995 request, was the six percent increase in AIDS research funding distributed among Institutes based on scientific criteria and according to priorities articulated in the strategic plan?

Dr. Fauci: The FY 1995 request was developed based on the FY 1995 HIV-Related Research Plan and reflects a six percent increase NIH-wide. Upon receipt of the FY 1995 appropriation, resources will be distributed according to the FY 1995 HIV-Related Research Plan to the extent possible. The plan contains ICD-specific plans and projects, and provides a comprehensive plan for the expenditure of FY 1995 NIH AIDS research funds.

MICROBICIDES

Ms. Lowey: I understand that NIAID is taking a leadership role in the research relevant to the development of topical microbicides. What are the reasons for developing female controlled chemical barriers to prevent STDs and HIV infection?

Dr. Fauci: A consensus has emerged, in the context of the recommendations from four recent international conferences on microbicide development, that safe, effective, female-controlled chemical barriers are urgently needed to prevent sexually transmitted HIV infection and other STDs. The mechanical and chemical barriers currently available have many limitations. Although the male condom is capable of providing a very effective barrier against the transmission of HIV and the discharge diseases, its use requires the active cooperation of the male partner and therefore cannot be independently implemented at the discretion of the female partner. The female condom, on the other hand, requires the male partner's consent, and virtually nothing is known about its efficacy in preventing viral and bacterial STDs. Existing chemical spermicides have activity *in vitro* against most STD pathogens, including HIV; however, no clinical studies have yet been carried out which demonstrate unequivocally that spermicides prevent HIV infection. Moveover, several studies have revealed that spermicides can cause mucosal erosions and ulcers; whether these lesions might increase the risk of HIV infection is presently unknown.

Furthermore, there are many situations in which personal, social or cultural attitudes interfere with a woman's ability to negotiate and implement the use of barriers which could decrease the risk of infection. Specifically, the need for a method which can be implemented by women is grounded in the high prevalence of sex without condom use, risky sexual behavior on the part of one partner without the knowledge of the other, and non-consensual sex.

Just as oral contraceptives have dramatically increased the ability of women to avoid unwanted pregnancy, effective vaginal microbicides would enhance their ability to avoid sexually transmitted infections. Moreover, chemical barriers which inactivate pathogens in vaginal/cervical secretions as well as in the ejaculate could reduce female-to-male as well as male-to-female transmission. There is an urgent need for such products, in both developed and developing societies, to provide an alternative for those who either cannot or will not use condoms.

Because of the influence of STD co-infection on the risk of HIV transmission, microbicides which inactivate not only HIV but also *Neisseria gonorrhoeae*, Chlamydia trachomatis and the agents of genital ulcer disease would substantially enhance their potential to make an impact on the HIV epidemic. It is possible to demonstrate mathematically that a microbicide with 90 percent efficacy against HIV without any spectrum of activity against other sexually transmitted pathogens would be less effective than a product with 50 percent efficacy against HIV and a similar efficacy against other sexually transmitted pathogens.

Ms. Lowey: What level of funding is the NIAID committing to topical microbicide research?

Dr. Fauci: In FY 1994, NIAID will spend approximately $5,370,000 on Topical Microbicide research, and $12,110,000 is included in our FY 1995 President's Budget.

WOMEN'S INTERAGENCY HIV STUDY

Ms. Lowey: What is the commitment of the NIAID to the Women's Interagency HIV Study (WIHS) and the Women's Natural History Study?

Dr. Fauci: The study of HIV infection in women is a major research focus of NIAID. The NIAID funds several longitudinal cohort studies of HIV transmission and progression of disease in women. The Women's Interagency HIV Study (WIHS) and the Centers for Disease Control and Prevention's HIV Epidemiology Research Study are components of a multicenter longitudinal prospective cohort study to investigate the progression of HIV disease in women.

The WIHS is conducted at six sites; Bronx, New York; Brooklyn, New York; San Francisco, California; Los Angeles, California; Chicago, Illinois; and Washington, D.C. The project is studying the signs and symptoms of HIV infection in women, describing the pattern and rate of their immune system decline and examining potential information on the effect of therapies on the length of survival and quality of life for HIV-infected women.

Ms. Lowey: Will the NIAID ensure that funding for the Women's Interagency HIV Study is adequate to provide this critically needed data?

Dr. Fauci: Longitudinal studies such as the WIHS are ideal settings for research on the fundamental biology of HIV disease because they provide the ability to correlate basic research findings with clinical outcome. Such studies also provide the foundation for studying a number of important population-specific biological and clinical features of the epidemic, including the changing natural history and spectrum of complications of HIV disease in women. NIAID is committed to the continued support of this important study.

WOMEN AND MINORITIES IN HIV TREATMENT TRIALS

Ms. Lowey: What is the Institute doing to ensure that women and minorities are included in the HIV treatment trials?

Dr. Fauci: The participation of specific populations in NIAID-funded clinical trials reflects the changing demographics of HIV infection and AIDS. This illness initially affected homosexual and bisexual men but is currently pandemic, with increasing incidence in women and minorities. Enrollment of underrepresented populations is a high priority in NIAID-sponsored HIV treatment trials. Specific activities in this area include the Terry Beirn Community Program for Clinical Research on AIDS (CPCRA) program, which has dramatically increased NIAID's enrollment of underrepresented minorities and women in HIV therapeutic trials; establishment of four AIDS Clinical Trials Units (ACTUs) at minority institutions: Howard University (Washington, D.C.), Meharry Medical College (Nashville, TN), University of Puerto Rico (San Juan), and the University of Hawaii (Honolulu); establishment of Women's Health Committees within the Adult Clinical Trials Group (ACTG) and CPCRA organizations; provision of supplements to the ACTG for outreach activities towards these populations; implementation of institutional evaluations of progress in achieving recruitment goals at ACTG and CPCRA sites to ensure participation of underrepresented populations; ongoing commitment to the establishment of community advisory boards for each ACTG and CPCRA site; and establishment of NIAID's AIDS Research Advisory Committee task force on underrepresented populations in clinical trials.

HISPANICS AND THE NIH

Mr. Serrano: Dr. Fauci, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Fauci: NIAID is involved in the development of an NIH-wide plan to increase participation of Hispanics in all phases of biomedical research, including Hispanic representation in the NIH workforce. This is the outgrowth of the September 1993 meeting held at NIH, under the sponsorship of NIH Office of Research on Minority Health, between the Hispanic Inter-American College of Physicians and Surgeons and representatives from NIH. NIAID sent a representative to the meeting who made a presentation on the various scientific programs contained within the Institute and the extramural programs it supports. Following that meeting, a 13-page report was prepared, containing recommendations to the NIH on a broad range of activities including increased hiring of Hispanics. NIAID will work with the NIH in incorporating the adopted suggestions within its various "pipeline" programs, such as the "Bridging the Career Gap for Underrepresented Minorities" initiative, and in its recruitment and hiring efforts.

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Fauci: In FY 1995 NIAID estimates that it will devote 2.9 percent, or $33,081,000 of its total resources towards research in health areas that impact Hispanics.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Fauci: NIAID supports three NIH-wide minority training programs: Minority Biomedical Research Support (MBRS), Minority Access to Research Careers (MARC), and Research Centers for Minority Institutions (RCMI). Approximately 40 percent of these awards are made to Hispanic populations. In addition, we have two "pipe-line" programs that are solely the creation of the NIAID: The Introduction to Biomedical Research and the Bridging the Career Gap for Underrepresented Minority Researchers programs.

The Introduction to Biomedical Research Program (IBRP)

This program is divided into two phases. Phase I is an affirmative action initiative and is designed to inform academically talented college juniors, graduating seniors, and first-year graduate or medical students from underrepresented minority groups about career opportunities in the broad field of biomedical research. This initiative grew out of the need to increase the number of minority scientific researchers in this country. This first phase consists of a series of scientific small group lectures, interviews, and a tour of the NIH Clinical Center and the National Library of Medicine. Students have the opportunity to discuss current research initiatives, scientific advances, and career concerns with our intramural scientists. The four-day conference is held annually in February at the Bethesda campus of NIH. NIAID provides resources for the entire program, including room, board, and airfare from their home institutions for the participating students. 59 students participated in Phase I in FY 1994; 25 percent of the students were from Hispanic backgrounds.

Phase II of the program, the NIAID Summer Program, is designed for college students in their junior year or graduating seniors planning to attend graduate or professional school in the fall. First-year graduate or medical school students with an interest in gaining actual work experience in the field of biomedical research also are sought for participation in this segment. Phase II is held from mid-May through September. Eligibility requirements are similar to Phase I, except that this program is not limited to minorities. However, annually between 45 and 55 percent of the selected students have been from minority or ethnic origin backgrounds. The program provides students with ten weeks of biomedical research training in one of NIAID's highly productive intramural research laboratories. Laboratories are located in Bethesda, Rockville, and Frederick, Maryland, and in Hamilton, Montana. The mentor system is used, and career counseling is offered. Attendance at research seminars is encouraged, and students often present their research projects to peers and specialists in their particular field of interest. In FY 1994 21 students were selected, 33 percent of which were from Hispanic backgrounds.

Bridging the Career Gap for Underrepresented Minority Researchers

This program was developed to bring underrepresented minority investigators, currently supported by the NIAID under various training and research supplemental awards, to the NIH campus for a two-day seminar. The NIAID, with the collaboration of the NIH Office of Research on Minority Health, sponsored this new initiative. The purpose of this seminar is to allow for the exchange of science; to impart information on applying for research project grants; to acquaint the participants with the opportunities and options open to them in the field of biomedical research; and to provide an opportunity to meet with NIAID intramural and extramural staff for the purpose of establishing mentors. The program is also an attempt to let these young researchers know that the NIAID has a vested interest in their academic future through the establishment of a "bridging program." The first seminar was held in October 1993 and had 48 participants; 25 percent were from Hispanic backgrounds.

Mr. Serrano: Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Fauci: NIAID has been at the forefront of recruiting minorities into its various clinical trials programs. Within its AIDS Clinical Trials Network, the percent of Hispanics participating in these trials in 1993, 16.2 percent, nearly mirrors the percent of AIDS cases in Hispanic populations in the United States, 16.7 percent. In addition, NIAID has added an Hispanic arm to its National Cooperative Inner City Asthma Study and, in collaboration with the Office of Research on Minority Health, has initiated a study of HLA genes focusing on Hispanics to improve organ transplantation tissue matches in this population. In addition to these ongoing efforts, NIAID plans to fully implement the new guidelines for inclusion of women and minorities in clinical research, including clinical trials.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Fauci: The NIH overall has great difficulty in the collection of racial and ethnic background of its grant applicants. While the grant application requests that the applicant self-identify their racial/ethnic background it is not a requirement, therefore data across the NIH is lacking. The NIAID did attempt a study of the racial/ethnic composition of its grant portfolio in FY 1991. By extrapolating from the FY 1991 data, the estimated number of Hispanic scientists who applied for an NIAID grant in FY 1993 would have been very low (36 out of a total of 2,048), and consequently the number of Hispanics who actually obtained funding (seven) was also proportionately low. The actual success rate for Hispanic scientists is in the order of 19 percent. NIAID believes that if the pipeline of Hispanic scientists were greater, the pool of Hispanics applying and obtaining a research grant would also be greater. This is why NIAID has invested in its own "pipeline-programs": The Introduction to Biomedical Research and the Bridging the Career Gap for Underrepresented Minority Researchers programs.

PEDIATRIC AIDS

Mr. Serrano: Dr. Fauci, as you know, my Congressional District in the South Bronx has the highest rate in the nation of HIV infection in children. I applaud the work you and your colleagues have done in this area, and I would be very interested in any advances NIAID or NIH has made in preventing and treating AIDS in children. Will you bring me up to date?

Dr. Fauci: An estimated 1,600 children are infected with HIV yearly in the United States, with about 10,000 children currently infected. Most of these children will develop AIDS. HIV disease in children tends to follow a more aggressive course than HIV in adults. In very young children, HIV progresses more rapidly, and the range of opportunistic infections (OIs) differs from that in adults. For example, more bacterial infections compared with other OIs are seen in HIV-infected children. Furthermore, the immunosuppressive effects of HIV are superimposed on immature immune and nervous systems, leading to a wide range of developmental problems affecting many vital organs.

The primary goal of the NIAID research on pediatric HIV disease is to identify and support the development of improved interventions to prevent and treat HIV infection and its sequelae in infants, children, and adolescents.

Perinatal transmission is responsible for most HIV infections in children in the United States and the rest of the world. The recent results from the NIAID sponsored ACTG 076 clinical trial demonstrated a 67 percent reduction in the transmission of HIV from pregnant mothers to their infants when the mother received AZT during pregnancy and the infant was treated for the first six weeks of life.

This trial was conducted by the Pediatric AIDS Clinical Trials Group in collaboration with the National Institute of Child Health and Development-sponsored clinical trials sites. NIAID is committed to the continued support of the Pediatric ACTG for the conduct not only of perinatal transmission trials but as a primary means of facilitating clinical trials of HIV therapies for children.

The Pediatric ACTG is currently placing an emphasis on research related to prophylaxis against OIs. One of its highest priorities is a multiple opportunistic pathogens study for the prevention of bacterial infection, *Mycobacterium avium* complex and *Pneumocystis carinii* pneumonia (PCP) using TMP/SMX, azithromycin and atovaquone. Additionally, prevention of PCP remains a high priority. Two studies, using atovaquone (Phase I) and dapsone (Phase I-II), are currently addressing this pathogen. Finally, a Phase I study of oral ganciclovir for prevention of serious cytomegalovirus infections in children is under development.

Protocols addressing prevention of measles, varicella-zoster, and herpes viruses are all under development.

Mr. Serrano: Are the AZT results promising enough that we should consider putting more FY 1995 resources into Ryan White Title IV--into outreach, testing, counseling, and care for HIV-positive pregnant women--to protect their babies?

Dr. Fauci: ACTG 076, an NIAID-sponsored study demonstrated a 67 percent reduction in the transmission of HIV from pregnant mothers to their infants when the mother receives AZT during the pregnancy and the infant is treated for the first six weeks of life. As a result of these data and at the direction of the Assistant Secretary for Health, a Public Health Service (PHS) task force has been formed to develop PHS policy regarding the use of AZT to prevent perinatal transmission. This task force will be considering policy implications for testing/screening, counseling, outreach and other aspects of care for HIV-positive pregnant women.

ASTHMA

Mr. Serrano: At the time of last year's hearing, Phase I of the National Cooperative Inner-City Asthma Study was expected to end in March 1994, and preliminary results were expected to be available in the fall of 1993. What are the most recent findings available from Phase I?

Dr. Fauci: The National Cooperative Inner-City Asthma Study (NCICAS) is an eight-center study of inner-city children, four to nine years of age. Phase I is designed to identify risk factors for severe asthma.

Over 1,500 Phase I study participants have had a comprehensive medical examination at one of the eight study clinics which included pulmonary functions, allergen skin tests, and urinary cotinine. Extensive data have been collected on patient-physician communication in the emergency room including: the analysis of over 100 emergency room tapes, asthma knowledge of caregivers, and psychosocial measures. Study participants were followed at three, six, and nine months to monitor asthma severity prospectively. Home environmental surveys measuring allergen exposure and home nitrite levels were completed on over 660 homes. In addition, a serum bank has been established on Phase I study participants. Plans for the analysis of Phase I data have been completed and these analyses will begin in the summer of 1994, with preliminary findings available by the end of 1994. Analyses of these data are anticipated to show the importance of appropriate medical and environmental influences on asthma.

Mr. Serrano: What will the second phase include?

Dr. Fauci: Phase II, which is now underway, and will involve recruitment of 1,000 inner-city children for a controlled intervention trial intended to reduce risk factors for severe asthma identified in Phase I and, consequently, reduce asthma morbidity in this population. A two-pronged intervention is planned: a case manager to assist the asthmatic in obtaining appropriate care, and modification of home environment to reduce the environmental triggers of asthma, e.g., host dust mites and animal dander.

LYME DISEASE

Ms. DeLauro: The FY 1994 Appropriations House Report contained language that "encourages NIAID to investigate in a systematic fashion whether chronic Lyme disease is an infectious or post-infectious disorder and to report to the Committee prior to the 1995 hearings on how this will be accomplished." The report language also "commends NIAID on its efforts in the development of direct tests for Lyme disease and encourages an expansion of resources devoted to applying these techniques in the investigation of the etiology of chronic Lyme disease and appropriate treatment for it." Do you have a plan for investigating whether chronic Lyme disease is an infectious or post-infectious disorder?

Dr. Fauci: NIAID is supporting a number of research grants to examine chronic or late stage Lyme disease and the numerous "post-infection" sequelae associated with Lyme disease infection. Recently developed methods to detect *Borrelial* DNA in patient body fluids suggest that persistent infection is a major reason for some chronic complications associated with Lyme disease. However, the detection of spirochete DNA in patients previously treated with antibiotics has not yet ascertained whether this detected DNA represents dead or living spirochetes, or fragments of spirochetes. Ongoing research should clarify the issue. However, confirmation of the persistence of Lyme *borrelia* in patients does not preclude the possibility that immunologic and inflammatory responses play a significant role in the course and severity of disease in many patients. Persistent infection, along with aberrant immune and inflammatory responses, are not mutually exclusive complications to Lyme infection. Research applications received in response to our 1994 solicitations for animal models of chronic Lyme disease, and immune response to Lyme infection and vaccination, should greatly expand our ability to elucidate the underlying mechanisms of chronic Lyme disease.

Ms. DeLauro: How many awards do you anticipate will be made in FY 1994 and FY 1995 in order to further research into this question?

Dr. Fauci: The NIAID currently supports 38 research projects on Lyme disease, including two intramural studies at the Rocky Mountain Laboratories. Before the current fiscal year ends we hope to make approximately six to eight additional awards to study immune responses to Lyme infection and vaccination. In addition, we hope to make two, possibly three, contract awards to support research on animal models of chronic Lyme disease.

Ms. DeLauro: How much will you spend on Lyme research in FY 1994 and FY 1995?

Dr. Fauci: NIAID will spend approximately $10,302,000 on Lyme research in FY 1994, and $10,640,000 is included in our FY 1995 President's Budget.

Ms. DeLauro: In your budget justifications, you indicated that NIAID-supported investigators recently examined the cost-effectiveness of parenteral antibiotic treatment of patients with a positive serologic test for Lyme disease, and they concluded that for most such patients whose only symptoms are nonspecific myalgia or fatigue the risk and costs of antibiotic therapy exceed the benefits. Only when the "value" of patient anxiety about leaving a positive test untreated exceeds the cost of such therapy is the empirical treatment effective. How was this patient anxiety "valued" and how was it determined when that value exceeded the cost of therapy?

Dr. Fauci: A study was recently conducted on the cost-effectiveness analysis of empiric parenteral antibiotic treatment of patients with nonspecific constitutional symptoms and its results published in the 1993 Annals of Internal Medicine, which concluded that when the patient's anxiety (chagrin) about not treating a positive Lyme titer exceeds $3,500 do the benefits of that strategy exceed the risks. A dollar value was not actually intended to be assigned to individual patient anxiety about infection and treatment. The study's statement was intended only to indicate the low probability of intravenous therapy being beneficial to many patients, given their symptoms and the risks incurred by intravenous drug therapy. Similar views of parenteral treatments are supported by the American College of Rheumatology and the Council of the Infectious Diseases Society of America. Their joint policy statement concluded that in patients whose only evidence for Lyme disease is a positive immunologic test, the risks for empiric, intravenous antibiotic treatment outweigh the benefits.

Ms. DeLauro: A recent study published by Erica Asch et al., found that despite recognition and treatment, Lyme disease is associated with significant infectious and post-infectious illness--over 50 percent of the people studied had persistent symptoms of arthralgia, arthritis cardia, or neurologic involvement with or without fatigue. Does this suggest that chronic lyme, whether it is in fact caused by chronic infection, or is a post-infectious disease, may be a trigger for CFIDS or fibromyalgia, or similar disorders?

Dr. Fauci: Dr. Asch's study, published in the Journal of Rheumatology, March 1994, examined 215 patients in the Westchester County area, and it was concluded that Lyme disease is associated with significant infectious and postinfectious sequelae. Fatigue and arthralgia were among the noted sequelae, or chronic complications. The article went on to suggest that Lyme disease patients may sometimes develop generalized pain and/or fatigue following infection. Symptoms of fatigue should not be confused with Chronic Fatigue Syndrome (CFS). Both CFS and Lyme-associated complaints of persistent fatigue are distinguishable on the basis of a variety of clinical features that include neurologic, musculoskeletal, and serologic characteristics.

MICROBICIDES

Ms. DeLauro: What level of funding is NIAID committing to topical microbicide research in the current fiscal year, and what level will be committed in FY 1995?

Dr. Fauci: In FY 1994 NIAID will spend approximately $5,370,000 on Topical Microbicide research, and $12,110,000 is included in our FY 1995 President's Budget.

Ms. DeLauro: What level of resources will be devoted to the three parallel tracks of research--basic science, product development, and clinical evaluation--that were identified as being necessary at a conference NIAID held jointly with the National Institute of Child Health and Development?

Dr. Fauci: NIAID will support the three parallel research tracks identified above. The research areas are all critical and complementary aiming at the development of safe, effective topical microbicides. In FY 1993 much of NIAID topical microbicide funding was spent on basic research. This basic biomedical research defines the molecular basis and chronology of the early steps in the infectious processes and also defines the vaginal and cervical ecology and the natural defense mechanisms of the female reproductive tract. In Fiscal Years 1994 and 1995, NIAID will dedicate a great deal of funding towards clinical evaluation and product development. Through product development research, NIAID will evaluate candidate topical microbicides through appropriate laboratory and pre-clinical testing strategies. NIAID will conduct research aimed at facilitating the development of STD diagnostic tests. These tests will enable clinical research on microbicide evaluation to proceed rapidly and contribute significantly to reducing the costs of the clinical evaluations. Our goal is to allocate approximately 50 percent of the topical microbicide research funds to basic research, 35 percent to clinical evaluation, and about 15 percent of the funding to product development. This balance reflects the NIAID objectives that are necessary for the development and delivery of safe effective topical microbicides.

Ms. DeLauro: Will it be possible to develop a microbicide that is not spermicidal?

Dr. Fauci: A number of promising approaches are on the horizon. A wide range of substances have properties which suggest that they may have potential as vaginal microbicides. It is conceivable, moreover, that the use of two or more agents in combination, if chosen judiciously, will prove more effective and less toxic than one agent on its own. The inclusion of substances to control the vaginal pH could also be important in view of the above evidence that HIV can be inactivated *in vitro* by low pH.

It is noteworthy that the bacterial cell membrane contains unique lipids which can be specifically solubilized by certain detergents which do not seriously affect the membranes of eukaryotic cells. Thus such detergents may be interesting candidates for use as vaginal microbicides. Their primary action would be against bacterial pathogens, therefore, they may fall short of expectations for microbicides active against HIV. However, it is possible that these products may work effectively and safely against infection by HIV--including cell-associated virus--by combating sexually transmitted diseases that increase the risk of HIV transmission.

Diverse non-surfactant substances appear to be plausible candidates as intravaginal agents. Some sulphated polysaccharides, although not virucidal, are of considerable interest as potential intravaginal agents. This is because they have been shown to block an early stage of HIV infection (either the virus's interaction with its cell-surface receptor or its entry into the cell) and also to prevent the formation of syncytia between HIV-infected and uninfected cells.

Evidence has been published that myeloperoxidase can kill HIV, and a commercial product containing both this enzyme and eosinophil peroxidase is available. Whether this approach will be effective in preventing the sexual transmission of HIV is likely to depend upon whether such enzymes can be made available in a formulation in which they will be active in the genital secretions. Another commercial product, Povidone-iodine (Betadine), frequently used as a hospital disinfectant, can also inactivate HIV.

As already mentioned, HIV is unstable at low pH. Acidic preparations are available commercially as pH adjusters for vaginal use (e.g., a gel containing acetic acid buffered at pH 4-4.5), but their value in preventing HIV infection has not been demonstrated.

The administration of specific antibodies vaginally to block HIV transmission is a theoretical possibility, but this approach has not been tested experimentally.

Ms. DeLauro: What is the need for this type of product?

Dr. Fauci: The need for a microbicide that is not spermicidal is based on the following:

There are currently four female-controlled methods which effectively prevent pregnancy, whereas there are no methods which prevent infection while permitting conception. While a woman's contraceptive needs may change over a lifetime, so long as she is sexually active she will require and/or desire protection from infection. Non-contraceptive microbicides would be very useful to women ~~who~~ over this span of time.

Furthermore, the window between safety and toxicity may be greater if the microbicide does not disintegrate host cells (sperm); of course these non-contraceptive microbicides will have to be safe vis a vis embryogenesis and fertility.

SPERMICIDES

Ms. DeLauro: Is there concern about the safety of over-the-counter spermicides, and if so, what is NIAID doing to assess the safety and efficacy of over-the-counter spermicides for use to prevent STDs and HIV?

Dr. Fauci: Existing chemical spermicides have activity in the test tube for most sexually transmitted disease pathogens, including HIV; however, no clinical studies have yet been performed that demonstrate unequivocally that spermicides prevent HIV infection. Moreover, several studies have revealed that spermicides can cause mucosal erosions and ulcers; whether these lesions increase risk of HIV infection is presently unknown. The following points are important:

- The active ingredients in commercial spermicides are detergents;

- The mechanism of action is disintegration of the host cell membranes;

- There is no specificity in this action; sperm cells, vaginal and cervical epithelial cells and enveloped (host-cell membrane) viruses; and

- The formulation may, in some products also be irritating.

In addition to the disintegration of membranes, other side effects include disruption of the vaginal ecosystem, i.e., killing of beneficial normal flora, overgrowth with yeast and gut pathogens, and alteration of mucous layer and pH levels.

The NIAID plans to fund a large clinical study in the Cameroon, which will be a randomized placebo-controlled study using a spermicide containing film. Two previous studies with this film have not shown an increase in genital lesions that have been shown with other formulations with higher concentrations of N-9. The other arm of the study will involve a film that does not contain N-9. Both groups will be counselled to use condoms and provided same, and the study will involve 1,500 HIV positive and negative women and will be conducted using rigorous safety evaluations.

In addition, the NIAID has solicited proposals for the study of over-the-counter spermicides and their efficacy in preventing HIV infection through its HIVNET International Master Contract. These proposals will be reviewed in the Spring of 1994.

YEARS OF PRODUCTIVE LIFE LOST

Ms. DeLauro: Using the standard calculation for Years of Productive Life Lost Prior to the Age of 66 (YPLL), is it true that the level for heart disease and cancer exceed that for AIDS? What is the greatest cause of YPLL in the United States?

Dr. Fauci: Based on information received from the Centers for Disease Control and Prevention, it is true that the levels for Years of Productive Life Lost Prior to the Age of 66 (YPLL) for heart disease and cancer exceeds that for AIDS. The greatest cause of YPLL in the United States is injuries.

Ms. DeLauro: What is currently the greatest cause of death among men ages 25 to 44 in the United States?

Dr. Fauci: Based on information received from the Centers for Disease Control and Prevention, AIDS is the greatest cause of death among men ages 25 to 44 in the United States.

AIDS

Ms. DeLauro: With respect to the AIDS/non-AIDS disparity in the NIAID FY 1994 budget that you described, is it fair to say that the non-AIDS component of the NIAID would not have been so adversely affected if the AIDS budget and appropriation had been consolidated, as has been requested this year? In other words, wasn't the NIAID non-AIDS program penalized, in effect, because of the size of the NIAID AIDS program and the decision to maintain a relatively even increase among all ICDs?

Dr. Fauci: It is difficult to speculate about the impact on NIAID's funding situation had the AIDS budget been consolidated in FY 1994. I can state, relative to your other question, that NIAID received an increase of over 18 percent between FY 1993 and FY 1994 for its AIDS/HIV portfolio. NIAID also received increases for other investments, e.g., vaccine and tuberculosis. Once all investments were removed from the budget, NIAID was essentially reduced by 7.5 percent. When the House and Senate wanted to ensure that all NIH ICDs received at least a 5.2 percent overall increase between FY 1993 and FY 1994, money was added to most of the other Institutes' nontargeted areas. Because NIAID's overall increase was more than eight percent, no additional money was added. In addition, when taking mandatory budget reductions in personnel and administrative costs, the non-AIDS budget had to absorb these reductions, further eroding the non-AIDS budget.

NATIONAL INSTITUTE ON DRUG ABUSE

PROGRESS IN DRUG ABUSE RESEARCH

Mr. Smith: NIDA funding has increased substantially since 1987, as part of a government-wide assault on drug abuse. Are you satisfied with the product of this investment in research?

Dr. Leshner: Progress in drug abuse research has been exceptional over the period since 1987. As a result of this research, for example, receptors have been identified for all major drugs of abuse. The first receptor for THC, the psychoactive ingredient in marijuana, was cloned in 1991 and the dopamine transporter, thought to be the primary site of cocaine's action, was cloned in 1992. The clinical implications of these discoveries are major. As we gain a better understanding of receptor structure, regulation, and function, their role in brain circuities associated with the brain's "reward" system should lead to faster development of new and improved therapies for addiction.

Scientists have developed an understanding of how abused drugs produce euphoria through activation of brain reward mechanisms and have shown that the addictive properties of abused drugs are mediated through sites which are anatomically distinct from those areas which mediate physical dependence. Such information will be critical to development of medications that block drug-induced euphoria but do not interfere with natural reward processes.

Mr. Smith: Can you point to new drugs, new therapies, and new prevention strategies that have been developed in the past seven years?

Dr. Leshner: L-alpha-acetylmethadol (LAAM) was approved by FDA in 1993 as a treatment for heroin addiction. It is the first new treatment medication for drug abuse in a decade and the initial fruit of NIDA's Medications Development Program, established in 1990. Other medications currently under development include: a long-acting dosage form of the narcotic antagonist, naltrexone; clinical trials of a mixed agonist/antagonist therapeutic, buprenorphine; and the discovery/development of medications to be used in the treatment of cocaine dependence.

Investigators supported by NIDA have also discovered anandamide, which is believed to be a natural ligand for the cannabinoid receptor and which may lead to the development of therapeutic drugs that have the medicinal effects of THC, the psychoactive ingredient in marijuana, without the adverse psychotropic effects. In other research, NIDA grantees have found that oral mecamylamine, a nicotine antagonist, combined with a nicotine skin patch, makes it significantly easier for people to give up cigarettes and to avoid relapse to smoking.

Drug abuse prevention research focuses upon testing under controlled conditions the efficacy and effectiveness of theory-based prevention programs. Of critical importance to prevention research is knowledge derived from etiologic and epidemiologic studies which identify those biologic, psychological, social, and environmental risk and protective factors associated with drug use onset and progression to abuse. This research identifies risk and protective factors that are malleable and that could be remedied or strengthened with the introduction of a drug prevention program focused upon theory-based constructs.

Etiologic research has identified a number of temperament, familial, personality, peer-related and social/environmental conditions that may be precursors to the development of drug abuse, such as aggressive behavior, emotional distress, alienation and rebelliousness, social competence, anti-social behaviors, poor family management practices, low bonding to family, low commitment to school, and association with drug-using peers. Research indicates that focusing solely on the individual is an insufficient means of preventing drug use. Family, neighbors, peers, friends, teachers, and others in the social environment who encourage and reinforce positive behavior changes play a vital role in prevention.

Prevention research assesses how to structure and strengthen social environments to promote positive, self-regulated health behavior. Prevention research studies indicate that comprehensive strategies that use combinations of mass media, schools, family, peers, social networks, and health policies both to shape and reinforce self-regulated behavior change offer the best chance of preventing drug use behaviors for both general and high-risk populations. This research suggests that multi-level prevention programs are needed across the developmental life span.

The overall effectiveness of treatment in reducing drug abuse has been well established. Benefits such as the elimination of drug-related criminal behavior and improvement in social and health problems are also associated with treatment. The degree of effectiveness of a given episode of treatment depends upon individual factors and upon program factors. Matching patients to the appropriate treatments results in increased treatment engagement, retention, and compliance. For particular subgroups of patients there is reason to believe that particular types of therapies may be more useful than others.

There is evidence from Kadden and colleagues at the University of Connecticut that a structured, behavioral therapy may be more effective for substance abusers with sociopathic characteristics than an interactionally focused therapy. Woody and colleagues at the University of Pennsylvania have shown that in subgroups of patients with antisocial personality disorder who have an additional diagnosis of depression, cognitive-behavioral and supportive-expressive psychotherapy is of benefit. However, antisocial personality disorder alone appears to be a negative indicator for response to psychotherapy.

There is evidence (University of Pennsylvania) that the addition of psychotherapy to drug abuse counseling may be necessary for other subgroups of addicts. In a methadone-maintenance program, drug abuse counseling is a sufficient complement to the treatment of opiate addicts with low levels of psychiatric severity. Providing psychotherapy to low psychiatric severity methadone-maintained opiate addicts who are already receiving drug abuse counseling does not appear to yield any further benefit However, in methadone-maintained opiate addicts with high levels of psychiatric severity, psychotherapy in addition to drug abuse counseling is significantly more effective than drug counseling alone.

Drug abuse intervention can have a profound impact on reducing an individual's likelihood of HIV infection. In one study, every one of 641 IDUs on whom AIDS street outreach intervention research was performed reported sharing of non-disinfected injection equipment--needles, water, cottons--at the beginning of the study. After four years of direct intervention unsterile practices continued among only 14% of the group. The drop in high-risk injection practices resulted in the rate of new cases of HIV infection dropping from about 10% to about 2% annually. It is estimated there were only 90 seroconversions among the 641 subjects during the period--nearly 50% fewer cases of HIV infection than expected--as a result of the drop in use of non-disinfected injection equipment.

Future HIV prevention research efforts must build on past successes in reducing high risk injecting behaviors. Important areas of research include development of more effective interventions to reduce sexual risk behaviors in drug users to target IDUs who are resistant to risk reduction, to recruit high risk groups into treatment, to improve bleaching techniques among IDUs who continue to share needles, to assess alternative risk reduction strategies such as needle exchange, and to improve HIV testing and counseling approaches.

TRENDS IN DRUG ABUSE

Mr. Smith: The recent high school survey on drug use indicated a reverse in the trend of declining drug use among this population. The DAWN survey of emergency room admissions for drug abuse showed an upward trend. How should we interpret this data?

Dr. Leshner: Data on a nationally representative sample of twelfth graders have been gathered annually since 1975 by the Monitoring the Future Study, which assesses the values, preferences, lifestyles, and drug use patterns of American youth. Eighth and tenth graders were added in 1991. The 1992 survey, which covered nearly 50,000 students found statistically significant increases in the use of marijuana, cocaine, crack, stimulants, inhalants, LSD, and other hallucinogens among eighth graders between 1991 and 1992.

The trends reflect changing social norms and conditions and the dynamic nature of drug use behaviors. The investigators have previously shown that increases in the perceived dangers of using drugs have played a major role in reducing their use. It is, therefore, troubling that some of the key beliefs and attitudes among seniors have begun to move in the opposite direction, with a decline among seniors in the perceived risks of LSD, heroin, and amphetamines. Media attention on world events such as the Gulf War in 1991 and other events (e.g., downfall of communism in eastern Europe) seems to have diminished the impact of advertising campaigns directed towards the use of illicit drugs, which had a major impact on young people in the 1980s. The major issues of the 1990s seem to focus more on topics such as health care, the economy, and crime and less on illicit drug use.

With regard to the DAWN data, with the purity of heroin and cocaine rising and prices remaining relatively low, it is not surprising to observe the increases in emergency room admissions. Many of these persons are over 35 years old and represent chronic users who overdosed or are seeking detoxification.

Mr. Smith: Does this call into question the effectiveness of our current treatment and prevention programs?

Dr. Leshner: These data do not call into question the effectiveness of existing programs, but rather stress the need for increased research into understanding better the biological and human dynamics of drug abuse and the complex interplay of biomedical, behavioral, and social factors.

Mr. Smith: Why is your Institute continuing to fund some surveys, like the high school survey, when other data collection has been transferred to the Center for Substance Abuse Treatment?

Dr. Leshner: The National Household Survey on Drug Abuse, DAWN, and the Client Data System were transferred to the Office of Applied Studies within SAMHSA. The high school survey is a component of the broader Monitoring the Future Study, a research study which includes a longitudinal as well as a cross-sectional design. The Monitoring the Future Study provides critical information on causes, consequences, and correlates of drug abuse, as well as information on impending drug problems that can be used for prevention research planning in NIDA as well as for studying etiologic and epidemiologic factors over time, changes in progression and continuation, and attitudes. The Monitoring the Future Study is an investigator-initiated research project supported under the regular project grant mechanism.

MEDICATIONS DEVELOPMENT

Mr. Smith: A recent Institute of Medicine report characterized the state of knowledge in addiction research as "rudimentary." Is this a fair critique?

Dr. Leshner: Given that drug addiction is not a simple physical disease with one cause, but a complex biological, behavioral, social, and psychological problem which must be approached at a multidisciplinary level, it is remarkable that addiction research has progressed so far in the last few years. Identification and cloning of receptors for all of the major drug classes, the development and FDA approval of two new treatment drugs, and contributions to the "human brain mapping" project are not the marks of rudimentary research efforts.

In fact, there is a considerable body of knowledge about opiate addiction, and NIDA's research program in general was given a most favorable review by the IOM. The IOM report however correctly pointed out areas where more research is needed. In particular, the report cites gaps in knowledge about the pathophysiology involved in protracted abstinence and relapse; the need for knowledge about the basic mechanisms of cocaine addiction, the genetics of vulnerability to addiction, and the bases for chronic drug effects; and the need for laboratory models of behavioral characteristics. The report also points out that "unless basic research is supported at an appropriate funding level, it will be difficult to make the necessary progress in the scientific knowledge base."

The following are just a few of the more significant research advances of the past several years, which have implications not only for drug abuse and addiction, but for the underlying behavioral and neuroscience aspects of many diseases under the purview of other NIH Institutes.

CLONING OF MULTIPLE OPIOID RECEPTORS

Following the successful cloning of the delta opiate receptor, the mu and kappa receptors have been cloned. The mu receptor is associated with euphoric and analgesic actions of opioids while delta and kappa are associated with analgesia. These discoveries should facilitate understanding of mechanisms of opiate action in addiction and pain control.

MORPHINE TOLERANCE BLOCKED BY INHIBITION OF NITRIC OXIDE SYNTHASE

Nitric oxide has been shown to be a novel neuronal messenger, and it appears to be involved in the neurotoxic action of certain drugs. Recent studies demonstrated that morphine tolerance mediated by the mu receptor can be blocked by an inhibitor of nitric oxide synthase--but not that mediated by kappa receptors. These studies may have relevance to both pain and addiction research.

NITRIC OXIDE MAY BE INVOLVED IN THE NEUROTOXICITY SEEN WITH AIDS

The inhibition of nitric oxide synthase can prevent the toxicity of gp120, the coat protein of HIV-1, to cortical neurons in culture. It is hypothesized that gp120 may trigger a cascade of events that activate nitric oxide synthase and the production of excessive nitric oxide which kills adjacent nerve cells.

BUPRENORPHINE MAY BE EFFECTIVE FOR TREATING HEROIN ADDICTION

The opiate partial agonist buprenorphine has been shown to be as effective as methadone in retaining patients in treatment. It also appears to have a more moderate withdrawal profile. NIDA is conducting a 12 site clinical trial of buprenorphine.

DEPOT NALTREXONE HAS BEEN DEVELOPED

NIDA has developed a subcutaneous depot injection of the opiate antagonist naltrexone. A tolerance/pharmacokinetic study has found no serious adverse effects. The depot system has been shown to be effective in blocking an challenge dose of morphine for a month.

COCAINE ANALOGS MAY BE USEFUL FOR TREATING COCAINE ADDICTION

PTT, a cocaine analog, was found to decrease metabolism in brain areas involved in addiction. PTT treatment resulted in substantial reduction in cocaine intake for the first 3 hours following administration.

COMMUNITY-BASED STREET OUTREACH PROGRAMS ARE EFFECTIVE
Community-based outreach programs have been found to be effective in recruiting hard-to-reach, not-in-treatment injection drug users and crack smokers. Studies have demonstrated that these programs facilitate behavior change, reduce needle and sex risk behaviors, and influence out-of-treatment users to seek drug treatment.

HIV PREVENTION IN TREATMENT SETTINGS EFFECTIVE
Studies show that even relatively small amounts of education and counseling can help many drug users modify their HIV risk behaviors. Drug abusers in treatment are at lower risk for seroconversion than those not in treatment.

TB IN HIV PATIENTS UNDERESTIMATED
Skin testing in HIV+ patients seriously underestimates the prevalence of TB infection. Since TB control in the U.S. relies on skin testing for identifying patients who should receive chemoprophylaxis, these findings have important implications. Chest X-ray may once again become a major screening tool.

NEEDLE EXCHANGE MAY REDUCE THE SPREAD OF HIV
An evaluation of the impact of the New Haven needle exchange program, using a system of labeling, tracking and testing distributed syringes, demonstrated a reduction of 33% in the incidence of HIV among regular needle exchange users. Further, 17% percent of regular needle exchange users are being referred to drug abuse treatment.

METHADONE DOSE IS FREQUENTLY NOT ADEQUATE
In a study of 700 outpatient treatment units, it was found that 34% of programs had average dose levels of 40 mg/day or less--despite evidence suggesting that low dose methadone maintenance is more likely to be associated with continued drug use. Despite widespread agreement that such services as medical care, mental health treatment, employment counseling, and legal counseling are an important part of drug abuse treatment programming, less than half the programs provided such services.

COCAINE SPECIFIC COPING SKILLS TRAINING REDUCES COCAINE USE
Cocaine abusers who received Cocaine Specific Coping Skills training were found to be nearly twice as likely to achieve abstinence from cocaine than cocaine abusers who received standard treatment. The training addresses major as well as individual triggers to cocaine use and identification and development of alternative behaviors.

DRUG PREVENTION PROGRAMS ARE SUCCESSFUL
Assessment of several drug prevention programs demonstrated that comprehensive community/school-based drug education programs that include drug information, peer resistance training, positive peer role models, and promotion of anti-drug social norms reduce alcohol, cigarette, and marijuana use and that alternative prevention programs appear to be effective with high-risk youth.

PRENATAL EXPOSURE OF DRUGS AFFECTS REPRODUCTIVE FUNCTIONS
Exposure to drugs during prenatal development has long-term, selective and gender specific consequences on reproductive functions. Binding of cocaine to spermatozoa, as well as evidence that offspring of cocaine-treated male rats exhibit behavioral alterations, raises concern that paternal drug use may alter the offspring.

Mr. Smith: The report further states that only two new anti-addiction drugs have been developed since methadone in the 1960s. When is it reasonable to think that the medications development program will produce new drugs?

Dr. Leshner: FDA and pharmaceutical industry experience has shown that new drug development can take up to 10 years per drug, depending upon a variety of factors. NIDA's Medications Development Division has brought out LAAM in three years by capitalizing on a large existing data base, and hopes to have buprenorphine, an opiate partial agonist medication (currently in Phase III trials) available in 1996.

In addition to looking for entirely new investigational drugs, NIDA is testing a variety of currently marketed prescription drugs for potential use as anti-addiction medications. Since these medications have a considerable human safety data base already in place, any which prove efficacious in treating opiate and cocaine addiction could be tested and approved in approximately two to three years.

NIDA knows of no private entities that were willing to develop LAAM or any other product for the treatment of addiction to controlled substances entirely on their own. This reluctance is based on the pharmaceutical industry's projected much lower rate of return for such products versus that for other therapeutic indications which could be pursued. As the IOM report recognizes, the speed with which new medications for addiction could be brought about would be greatly enhanced by removing current disincentives for private sector investment and development.

COCAINE ADDICTION

Mr. Smith: Are there any treatments available yet for cocaine addiction?

Dr. Leshner: Although several compounds are being tested in early trials, there is no currently approved medication for the treatment of cocaine addiction. NIDA's Medications Development Division is developing the portfolio of clinical trials needed to discover and develop medications for the treatment of cocaine addiction. Among potential medications currently under review is amantadine, an antiviral, which has been found to reduce cocaine abuse in methadone maintained patients. Follow up studies are in progress.

There are however several promising behavioral therapies for cocaine addiction that are being developed by NIDA grantees. Some examples are the following:

Higgins and colleagues at the University of Vermont are using a contingency management approach in which cocaine-abstinence is rewarded with social, occupational and family reinforcers, and in which cocaine use results in loss of reinforcers. This behavioral therapy is reported to be significantly more effective than the standard twelve-step approach in helping patients achieve initial abstinence from cocaine.

Another study demonstrated that a cognitive psychotherapy, known as Relapse Prevention, helps patients maintain therapeutic gains following treatment. Carroll and Rounsaville at Yale University found that cocaine abusers provided Relapse Prevention and those who were provided standard treatment did equally well during treatment. However, at six and twelve month follow-up, only those who had received Relapse Prevention were able to maintain the gains made in treatment.

Monti and Rohsenow at Brown University have shown that cocaine abusers who received a behavioral therapy called Cocaine Specific Coping Skills Training (CST) were nearly twice as likely to achieve abstinence from cocaine than cocaine abusers who received standard treatment. The investigators are now attempting to combine CST with Motivational Enhancement Therapy (a behavioral therapy shown to be efficacious with alcoholics) to determine if the efficacy of this combined treatment is greater than that for CST alone.

AVERAGE COST OF GRANTS

Mr. Smith: What is it about the nature of your research grants that makes them so much more expensive than the NIH average ($326,000 versus $240,000) or even other neurology grants?

Dr. Leshner: Although the average cost of basic research projects supported by NIDA is comparable to that of the other NIH Institutes, it is true that NIDA supported clinical research projects are much more expensive than the typical NIH project grant. NIDA research has demonstrated that the provision of comprehensive medical and other services at the time of drug abuse treatment can result in long-term savings both in medical and social costs. Accordingly, NIDA clinical research provides support for these services costs related to the research effort, and these services are expensive. NIDA also supports a growing number of community-based projects to explore methods for engaging and retaining out-of-treatment drug users in effective treatment. These studies require that staff be sent into the streets to find and encourage addicts to enter treatment studies, and that too is expensive.

Mr. Smith: Why does your 1995 budget assume such large increases for your new non-AIDS grants and centers (14.6 percent and 8.8 percent respectively)?

Dr. Leshner: The overall increase for competing research project grants (RPGs) in the 1995 request is held to the biomedical inflation index (+4.1%). However, because the proportion of AIDS projects to non-AIDS projects drops from 40% in 1994 to 20% in 1995 (due to the large increase in AIDS commitments generated in 1994), the increase in the average cost for the non-AIDS grants works out arithmetically to 9.1%, which together with the R18s converting to RPGs results in an average cost increase of +14.6%. In all likelihood the average cost of non-AIDS applications will be below the $326,000 projected using the biomedical inflation index, and NIDA will be able to award some additional non-AIDS projects, bringing the number of non-AIDS projects closer to the levels awarded in 1992 and 1993, before the drop that occurred in 1994.

With regard to centers, they too have been limited to a 4.1% increase. However, we have requested an additional $1 million to allow for supplements to continue the human clinical neuroscience initiative which is beginning in FY 1994.

Mr. Smith: Tell us more about the behavioral therapies development program you are launching. How will it be different from your current behavioral research?

Dr. Leshner: NIDA has supported studies of the efficacy of behavioral therapies through investigator-initiated research grants since the late 1970s. NIDA presently funds a number of research grants investigating various behavioral approaches including psychotherapy, behavior therapy, and counseling in the treatment of drug addicts. While considerable progress has been made in finding efficacious and clinically relevant behavioral therapies, a more systematic and coordinated approach is needed to more rapidly develop clinically relevant interventions.

Recognizing the importance of this area, NIDA has initiated a behavioral therapies research program that parallels NIDA's Medications Development Program. NIDA plans to expand and complement current efforts in order to systematically identify, define, standardize, establish efficacy, evaluate generalizability and transferability to community-based treatment programs, "endorse" and disseminate the most promising behavioral therapies.

The Behavioral Therapies Development Program will support three stages of behavioral therapy research. Stage I is an iterative process which involves identifying promising clinical and research findings relevant to drug abuse treatment, generating and formulating new psychobehavioral therapies, operationally defining the therapies in manuals, and pilot testing and modifying the therapies. Stage II research consists of highly controlled small-scale efficacy testing of promising therapies identified in Phase I. Stage II also involves the replication, at other sites, of efficacy studies with positive results. Stage III entails the larger-scale testing in multiple community-based treatment programs of therapies that have been shown to be efficacious in more than one controlled clinical trial in order to demonstrate transferability to community treatment programs and generalizability to diverse patient populations.

Mr. Smith: How much funding do you devote to behavioral versus biomedical interventions?

Dr. Leshner: Last year, in 1993, NIDA spent $105.0 million on behavioral/psychosocial treatment research compared with $52.7 million for research on pharmacologic (biomedical) intervention research.

CONFERENCES

Mr. Smith: According to a report recently transmitted to the Committee by the Department, your Institute spent more than any other in 1993 on conferences. Your $2.1 million total was almost twice that of the Cancer Institute, for example. Why do you need so much conference money?

Dr. Leshner: NIDA supports a number of meetings and conferences using the contract mechanism, and the $2.1 million cited in the PHS report includes not only the costs associated with meetings, but the full contract costs for other services as well, including writing, editing, and analysis of research data. Drawing together the diverse professional groups working on drug abuse is critical to developing a broad and culturally diverse perspective on drug abuse problems in this country and improving drug abuse prevention and treatment through research. The following conferences were supported with 1993 funding:

-- Three conference grants that provide a scientific forum where clinicians and basic scientists gather to discuss recent advances in drug abuse research, thus promoting collaboration between basic, epidemiologic, and applied research.

-- A Technology Transfer Conference, for the purpose of informing the professional drug abuse and HIV treatment and prevention community about recent advances in drug abuse research, with an emphasis on what works in drug abuse treatment and prevention and for which specific populations.

-- Eight special populations research development seminars to reach out to minority institutions and investigators and engage them in research on drug abuse and addiction.

-- Support for the Community Epidemiology Work Group meetings, which form the basis for NIDA's drug abuse surveillance system.

-- The Community Education on Research and Practice Program, directed to improving community response to drug abuse treatment and prevention.

ANIMAL RESEARCH

Mr. Smith: We have received inquiries from many people concerned with NIDA-sponsored research at New York University being conducted with animals by Dr. Ronald Wood. They contend that his research is irrelevant to human clinical needs and that he is mistreating his research animals. Please document the type of research Dr. Wood is conducting and its relevance, why the use of animals is necessary, and what steps have been taken to ensure that he is meeting NIH animal care standards.

Dr. Leshner: Dr. Wood is studying the deleterious effects of crack cocaine and abused inhalants on cardiopulmonary function. Because of how they are used, inhalants can quickly build up to toxic life-threatening levels. Dr. Wood's objective is to identify basic physiological changes induced by these drugs and to design new medications to limit or prevent their adverse effects.

In addressing the effects of inhalants, Dr. Wood has produced important and useful information in a research area noted for its difficulty. Most importantly, Dr. Wood has developed an animal model to examine the effects of inhalants. Animal behavior is highly reliable in predicting human drug use behavior. The animal model of inhalant abuse is important because it allows for studies into the basic pharmacology of inhalants that can not be carried out in humans. The model has demonstrated that inhalants are abusable substances, that they create drug-seeking behaviors, and that complex behavior required in the workplace can be impaired by inhalants. Without the type of information gathered in studies like those of Dr. Wood, it would be impossible to develop strategies aimed at limiting the injuries caused by these agents.

As with all research proposals supported by NIDA, Dr. Wood's projects have been reviewed for both scientific merit and appropriateness of animal use by two panels of non-Government experts. His research protocols have also been reviewed and approved by the Institutional Animal Care and Use Committee at New York University, which is required to include among its members a veterinarian, a researcher, a nonscientist, and a member of the community who is not affiliated with the University.

Mr. Smith: Have any special reviews been conducted in response to public concerns, either by NIH, the State of New York, or New York University?

Dr. Leshner: The NIH Office for Protection from Research Risks and the Department of Agriculture are currently conducting an investigation of a formal complaint brought by In Defense of Animals, an animal activist organization. Prompt corrective action will be taken if New York University or Dr. Wood is found to be in noncompliance with the regulations governing animal use.

Mr. Smith: In addition, please document the amount of NIDA funding received to date by Dr. Wood.

Dr. Leshner: Beginning in FY 1988 and through FY 1993, Dr. Ronald W. Wood has received a total of $1.6 million for his research on the behavioral pharmacology of crack cocaine.

MEDICATIONS DEVELOPMENT

Mr. Smith: Identify 1993-1995 medications development spending.

Dr. Leshner: The NIDA medications development program is a multifaceted effort that cuts across nearly all the divisions of the Institute, including the intramural Addiction Research Center in Baltimore: FY 1993 funding for this program was $52,733,000, and this is projected to increase to $56,600,000 in FY 1994 and to $60,300,000 by FY 1995.

Mr. Smith: How many drugs are in the Phase III clinical trial stage?

Dr. Leshner: Buprenorphine, a partial agonist medication for the treatment of opiate addiction has recently completed a Phase III efficacy study, and the data are now being analyzed for presentation to FDA.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject matter of research centers supported in 1994.

Dr. Leshner: NIDA supports both regular research centers (P50s) as well as developmental centers (P20s) and treatment research units (TRUs) which are being converted to P50s starting in FY 1994, and which are included in the centers line in the 1995 request documents. In 1993, NIDA supported the following research centers.

Basic Research -- three P50 grants
Behavioral Pharmacology -- three P50 grants
Neuroscience -- three P50 grants and one P20 grant
Prevention -- five P50 grants
Treatment -- eight P50 grants and seven TRUs

In addition to continuation of these centers in 1994, NIDA has budgeted for the renewal of a behavioral pharmacology center that did not receive support in 1993 and an additional neuroscience center in response to a special Request for Applications on clinical neurosciences that was released in January of this year.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. What is the significant role for this research in drug abuse research, elaborate?

Dr. Leshner: Genetic factors may play a role in determining individual responsiveness to drugs of abuse. Different inbred animal strains show differences in drug-related behavior. To date, no single gene defect has been associated with drug abuse, and indeed it is likely that a complex array of environmental and genetic factors affect vulnerability to drug abuse. Gene therapy therefore is not as prominent a potential therapeutic intervention in drug abuse as it is in other disorders of discrete genetic origin.

PAIN RESEARCH

Mr. Stokes: With regard to the pain research supported by the Institute, is there collaborative effort with the Dental Institute on the research that it is supporting in this area?

Dr. Leshner: In addition to investigations of the abuse of licit and illicit drugs, NIDA supports a significant portfolio of research to develop more effective pain relief medications and medications with less abuse potential. This research is coordinated with pain management research at the National Institute on Dental Research. This year, NIDA contributed to the support of a Dental Institute planning conference on research needs and opportunities in this area.

NEUROLOGICAL AND MOLECULAR BIOLOGY RESEARCH

Mr. Stokes: What are some of the most significant opportunities in drug abuse research that could be advanced through increased neurological research and molecular biology research, explain the benefits.

Dr. Leshner: Neurological research can be extremely valuable in revealing pathological phenomena which may relate to brain mechanisms affected by drugs of abuse. Understanding the causes and consequences of drug abuse requires knowledge not only of the immediate and long term actions of pharmacological agents but also of the complex cognitive and motivational processes underlying brain function, which lead to drug seeking behaviors. Some of the most significant opportunities in drug abuse research that would be advanced by neuroscience research are a much better understanding of:

--the neuronal circuits, pathways and structures within the brain that are directly affected by drugs of abuse;

--how these brain regions change in terms of chemistry, physiology and anatomy following repeated drug exposure and abuse;

Dr. Leshner: Drug addicts generally live very high risk and disordered lives and are sicker and die sooner than expected for persons of their respective age group. Among other medical problems, drug abuse is associated with the spread of HIV, hepatitis, and tuberculosis. Because drug dependent persons spend much of their time compulsively seeking illicit drugs, both job and educational opportunities are much more difficult to sustain, with cost consequences in the health, social, and criminal justice systems. The cost of treatment is far less costly than incarceration, and allows rehabilitation while reducing the spread of HIV, hepatitis, and tuberculosis.

By enrolling in NIDA sponsored clinical studies, addicts receive comprehensive medical examinations, counseling appropriate to the trial, and referral for services post trial. Importantly, they receive the benefit of attempting to break the cycle of addiction, rather than continuing in their same patterns. For clinic personnel participating in clinical trials, hope is generated that new medications will help them deal better with patients who have been unresponsive to current therapy. For example, many subjects in the LAAM trial report that they appreciate the more normal feeling that they get with LAAM. This is helpful in initiating and maintaining job and educational opportunities.

Mr. Stokes: To what extent has the Institute increased the number of minorities participating in its clinical trials? What progress is being made?

Dr. Leshner: Because drug addiction has been a significant problem in inner city populations, many NIDA-funded treatment research programs are located in these areas and serve significant numbers of minorities. Over the years NIDA has encouraged the inclusion of minorities in treatment research in all program announcements and requests for applications. For example, the recent Behavioral Therapies Development Program RFA specifically lists as an area of interest the development of "therapies that are culturally sensitive and address the unique needs and perspectives of minorities."

In 1989 and 1990, respectively, NIDA initiated treatment research demonstration project grants and treatment research units to improve the efficacy of drug dependence treatment to reduce the spread of AIDS. Demographic information from these programs indicates that minorities have been successfully recruited by these treatment programs and entered into clinical trials. On average 40-50% of the subjects were African American and 10-20% were Hispanic based on the last available reports from these sites. Several sites focused on minority populations (Washington, D.C., Baltimore, New York City, Albuquerque, Philadelphia, Kansas City).

It is NIH policy that minorities and women be adequately represented in late stage clinical trials unless there is strong justification for exclusion (i.e., not a disease of women, or occurs only in certain populations). NIDA follows this policy. In our last two large multi-center trials, the enrollments break out as follows:

LAAM:	33% female 29% African American 12% Hispanic
Buprenorphine:	32% female 22% African American 28% Hispanic

HISTORICALLY BLACK COLLEGES UNIVERSITIES

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of Historically Black Colleges and Universities in biomedical research?

Dr. Leshner: Recognizing the benefits to be gained by the scientific community and the community-at-large from the support of HBCUs engaged in drug abuse research and development, NIDA established an HBCU Task Force to develop a plan to increase the participation of HBCUs in NIDA's research programs. Three major areas of need were identified: (1) broad infrastructure support; (2) research experiences and mentoring; and (3) NIDA-wide support and staff training. The NIDA HBCU initiative addresses each of these areas.

One centerpiece of this effort is the establishment of centers for drug abuse research within the administrative hierarchy of the university, through which drug abuse research would be conducted. It is hoped that 4 to 5 such centers can be supported over the next 5 years. Research experiences can be made available to students and faculty, and a permanent place to conduct research will have been established. Other activities of the initiative include support for research training, summer research experiences, updating of a grantsmanship software package, and training for NIDA staff on minority programs.

MINORITY HIRING

Mr. Stokes: How many GS-15 and above positions are there in your Institute? How many employees in your Institute are in GS-15 and above positions?

Dr. Leshner: NIDA has sixty-six scientists and administrators employed at the GS-15 and above level. Currently there are two vacancies that NIDA is seeking to fill at this level.

Mr. Stokes: In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they?

Dr. Leshner: At the present time, NIDA has two African Americans at the GS-15 level, the Chief of the Survey and Analysis Branch, Division of Epidemiology and Prevention Research and a

Special Expert in the Community Research Branch, Division of Clinical Research.

Mr. Stokes: In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Leshner: No African Americans are among cases pending for exception to the freeze.

Mr. Stokes: Has the NIH requested relief from the freeze, if so, what was the response?

Dr. Leshner: NIH has appealed for higher FTE levels and a sparing of the scientific staff, in particular.

Mr. Stokes: If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Leshner: Lifting the freeze would enable NIDA to recruit nationwide. In support of recommendations made by the Secretary's Task Force on Black and Minority Health, NIDA has established the Special Populations Program and the Minority Recruitment and Training Program to provide training and support to minority students and scientists interested in drug abuse research and to assist NIDA in recruiting minority professional staff.

PREVENTION RESEARCH

Mr. Stokes: With Health Care Reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Leshner: Eggert and colleagues at the University of Washington tested the efficacy of the Personal Growth Class, a one semester drug abuse and school drop-out prevention program for high-risk youth in the ninth through the twelfth grades that fostered integrated group support and life skills development. Analysis of trend data from the pretest, post-test and five month follow-up indicates that students in the program report reductions in drug control problems and consequences, increases in grade point average, school bonding, and self-esteem, and reductions in deviant peer bonding.

In a series of controlled research studies, Botvin at Cornell Medical School tested the short and long-term efficacy of the Life Skills Training (LST) drug prevention program for middle school students. Program students report significantly lower levels of cigarette smoking, alcohol use, and marijuana use. Long-term follow-up demonstrates the potential durability of the effects produced by LST, with prevention effects lasting over a six year period.

Controlled prevention intervention research involving 42 treatment and control schools by Pentz at University of Southern California indicates that comprehensive, multiple component drug prevention programs can reduce adolescents' use of cigarettes, alcohol, marijuana, and other drugs. The Midwestern Prevention Project tested five interventions for 6th and 7th graders including media, drug education, parent training, community organization, and health policy promotion. Pentz reports that four-year follow-up results indicate a 24 percent reduction in monthly cigarette smoking, a 28 percent reduction in monthly alcohol use, and a 29 percent reduction in monthly marijuana use among students.

BIOTECHNOLOGIES

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Leshner: Research in biotechnology has provided the foundation for many of the advances in molecular biology which in turn have energized contemporary drug abuse research. By generating new techniques for manipulating genes and proteins, biotechnology has provided new tools to scientists in drug abuse research who are investigating basic mechanisms of brain function. Biotechnology has also provided new means of generating peptides and other proteins which are essential to the investigation of brain function and which may lead to the discovery of new therapeutic interventions. By devising new expression systems for receptor and other proteins, biotechnology also offers promise of new methodologies for the rapid functional screening of pharmacological agents. Biotechnology also offers promise for providing new techniques for understanding and mapping multigenic traits which may be important to understanding complex behaviors associated with drug abuse. Finally, biotechnology may provide new molecular techniques for devising novel delivery systems capable of accurately targeting pharmacological interventions to particular cell systems.

Mr. Stokes: As the Director of an Institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crises continues -- while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and -- while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Leshner: Drug abuse in this country is both a medical problem and a social problem. While much has been learned about individual vulnerability to drug abuse, and treatment and prevention strategies have been developed and applied that are culturally sensitive and effective for minority populations, many of the larger environmental and social problems that contribute to drug abuse are yet to be adequately addressed.

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Leshner: The problems of drug abuse and addiction require that the research workforce utilize biomedical, biobehavioral and psychosocial research tools. Further, there is a critical need for a diverse workforce, since minorities and women offer unique perspectives on drug addiction and related problems and may suffer disproportionately from these problems. Additionally, researchers who possess clinical experience are in high demand, and a variety of barriers, such as length and cost of training, and the nature of the patient population, have made the recruitment of research clinicians an arduous process.

The increased severity of the drug national problem has resulted in a significant increase in NIDA's research budget; however, the number of trained professionals who possess the requisite skills has not kept pace. NIDA must train more clinical and basic scientists to take advantage of the unique opportunities that have resulted from twenty years of research investment in drug abuse research. Towards this goal, NIDA has undertaken several initiatives to address this problem, but there is still much to be done. To bolster the ranks of drug abuse researchers, NIDA currently supports over 300 predoctoral and postdoctoral investigators through a variety of research training and career development mechanisms. These programs have been implemented as a means to increase the overall number and quality of junior investigators in the drug abuse research arena.

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Leshner: The increase in basic research knowledge concerning the human brain, its structures and neurochemical messengers is the most exciting and promising aspect for future clinical research. It is now possible to understand brain functioning in a manner which more rapidly leads to the development of potential medications for testing as potential medications. Scientists are more accurately able to predict which compounds should have an effect in the brain systems involved in addiction. Eventually it should be possible to "tailor make" molecules to have specific effects on the addictive process with minimal side effects on other biomedical processes.

In cocaine addiction, among the most exciting and promising discoveries are the investigations into the role of the biogenic amine transporter, dopaminergic modulators, and serotonergic modulators. It is now possible to perform non-invasive brain imaging to observe the effects of cocaine and potential treatment medications at an early stage. As this knowledge base increases, it should become easier to predict the potential for efficacy of potential treatment medications. The opportunity to clinically test basic research theories (such as the role of dopamine in cocaine addiction) is the opportunity to transform basic research into effective treatments for improving the Nation's health.

MINORITY INITIATIVES

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Leshner: NIDA works to ensure that our research program reflects the needs of minority populations in several ways. NIDA staff keeps itself informed of trends in minority health through familiarity with the major epidemiologic data sets on drug use. For example, the Monitoring the Future data on high school students, is used to examine rates by ethnicity. Other data sets such as the Household Survey and DAWN are similarly used. Drug Abuse Among Racial/Ethnic Groups is a monograph prepared by NIDA staff on drug use in minority groups. Information is solicited from outside scholars and researchers in minority health, through meetings held with the ongoing Hispanic Work Group and recently a meeting held with African American researchers. These interest groups provide NIDA with information on research needs and research training needs. Suggestions from scholars participating as mentors and trainees in the Special Populations Training Program are made available informally to NIDA staff and formally in reports. Information from these varied sources are used to shape the activities and research direction of our divisions.

NIDA initiates program announcements that emphasize areas of particular concern to minority health. For example, last year a PA on underserved populations was released, and NIDA received a large applicant response. We support minority research centers. For example, we have minority prevention research centers at Cornell Medical College and Colorado State in Fort Collins.

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your Institute?

Dr. Leshner: There are several initiatives in minority health research, research training and outreach supported by NIDA. NIDA supports minority research centers, in addition to Minority Institutions Research Development Programs (MIRDP) and the Minority Access to Research Careers (MARC) Program. NIDA supports MIRDPs at the Hispanic Research Center, University of Texas at San Antonio, Meharry College, Morris Brown, and SUNY, Old Westbury. These programs provide research experience and support to minority faculty and students.

Several years ago NIDA developed its Special Populations Mentoring Program. The program provides grantsmanship training to underrepresented scholars interested in drug abuse research. The goal of the program is to increase the number of underrepresented scholars applying for and receiving NIDA support for research projects, particularly R01 awards. Approximately 25 women and minority researchers participate in this program each year.

The Addiction Research Center (ARC), NIDA's intramural program, has developed a Minority Recruitment and Training Program which provides research experiences to minority students and faculty. IRTA (Intramural Research Training Award) fellowships are given to students who are at least 16 years old. They spend 8 weeks in the summer working with ARC scientists.

We have a Hispanic Work Group to provide recommendations on Hispanic health issues. Since 1989, NIDA has been working toward closer collaboration with the Hispanic drug abuse and HIV/AIDS community. In that year the Hispanic Research and Technology Transfer Work Group was created. It is composed of more than fifty Hispanic researchers, practitioners, and community leaders. The Work Group has developed and conducted five workshops for NIDA. The 1993 work group members developed papers on three policy issues. One paper focuses on the development of Hispanic researchers. There is still much to be done, and with the creation of a separate Special Populations Office in October 1993 in the immediate office of the Director, we hope to develop a more comprehensive and focused approach to increasing the numbers of Hispanic drug abuse researchers.

NIDA participates in programs sponsored by minority professional associations and schools in order to encourage interest in NIDA programs. For example, NIDA gives support to the Association of Minority Health Professions Schools' Annual Symposium on Career Opportunities in Biomedical and Public Health Sciences. About 1200 minority students attend the symposium. The chief of the special populations office participate in the panel on careers at NIH, and the EEO officer attend and meets students at the NIDA exhibit. NIDA supports the NAFEO conference, and has developed linkages with the National Medical Association and Black Psychiatrists of America. Outreach efforts are routinely made by our Community and Professional Education branch, which deals with technology transfer issues. National conferences have been held to focus on needs of particular minority populations.

Mr. Stokes: When your Institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health? To what extent is there a collaborative relationship between the two organizations, elaborate.

Dr. Leshner: Historically, there has not been much interaction between NIDA and the NIH Office of Research on Minority Health, because on in October 1992 did NIDA become an Institute of the NIH. In our first year as an NIH institute we responded to requests from the ORMH. Since then, we have sent a representative to the Chicago conference sponsored by the ORMH. With the establishment of our Special Populations Office we expect to become more involved with the ORMH on an ongoing basis..

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place?

Dr. Leshner: NIDA has made minority supplements starting as far back as 1991.

Mr. Stokes: Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Leshner: We have not kept track of the research careers of all our past minority supplement grantees. We do know that some of our awardees have become principal investigators on program projects. Tracking and interacting more with our minority supplement grantees is something we intend to do through our special populations office.

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Leshner: For 1994, NIDA expects to support $3,100,000 in awards to Historically Black Colleges and Universities.

Mr. Stokes: Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by Historically Black Colleges and Universities in the Institute's programs and activities?

Dr. Leshner: HBCU infrastructure and research experiences and mentoring needs are proposed to be met through contracts. One contract will provide intensive, long term technical assistance to a number of HBCUs to strengthen their capacity to competitively participate in NIDA's research program by addressing barriers to research participation. Aims of the program will be to provide technical assistance (in areas such as proposal development, gaining drug abuse research experience, negotiating release time, locating/accessing resources) matched to the level and needs of each HBCU and faculty member, to foster a relationship between NIDA and the schools by involving NIDA program staff and grantees in activities, and to encourage collaborative efforts across schools and with other NIDA supported investigators. Expected outcomes include an increase in research proposals submitted and funded, and an increase in the number of faculty and students who become involved in drug abuse and other areas of biomedical and behavioral research. This will also address the concern of having experienced minority investigators in the research pipeline.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Leshner: A breakout of NIDA's program follows:

Minority Training and Assistance

	FY 1993 ACTUAL	FY 1994 APPROP.	FY 1995 PRES. BUD.
HBCUs	1,267	3,100	3,300
Hispanic Initiative		500	500
MARC	117	150	200
MIRDP	129	150	200
Minority Recruitment & Training Program (IR)	50	98	100
Res. Supp. for Underrep. Minorities (ER)	1,384	1,400	1,600
	2,947	5,398	5,900

Historically Black Colleges and Universities. NIDA has recognized the contributions that Historically Black Colleges and Universities (HBCU) have made and can continue to make to the development of minority scientists and health professionals and in community education and prevention. NIDA therefore organized an HBCU Task Force in FY 1993, which proposed an HBCU initiative that will be implemented over the next five years. Support for the strengthening of infrastructures and for research training and experiences will be provided through several contracts and programs.

Hispanic Initiative. Based on meetings held with the Hispanic work group, a Hispanic initiative has been developed, with emphasis on technology transfer and research training.

Training and supporting minority investigators. NIDA encourages the use of available research and research training support mechanisms to increase the number of minority investigators pursuing drug abuse research. These include participation in the MARC, MIRDP, and minority supplement awards. In addition, in support of recommendations made by the Secretary's Task Force on Black and Minority Health, NIDA has established its own programs, the Special Populations Program and the Minority Recruitment and Training Program (MRTP), to provide training and support to minority students and scientists interested in drug abuse research.

Ms. Pelosi: In your testimony, you mention that multi-component drug prevention programs are more likely to be effective than more limited approaches. To what extent is your agency involved in valuating the outcome of drug abuse prevention programs?

Dr. Leshner: NIDA supports research to determine the efficacy and effectiveness of drug abuse prevention interventions implemented in schools, homes, communities, hospitals, or the workplace. Prompted by grant program announcements released by NIDA, drug prevention research scientists across the country are studying the efficacy of a variety of innovative, theory-based drug abuse prevention interventions both for general and high-risk populations. As part of our health services prevention research program, NIDA-funded researchers are testing the effectiveness of a number of drug prevention programs that are being implemented in a variety of service settings. The Prevention Research Branch supports 40 studies at a cost of $12 million.

Ms. Pelosi: How is the work of NIDA coordinated with the work of the Center for Substance Abuse Prevention and school-based drug prevention programs like the Drug-Free School program?

Dr. Leshner: NIDA coordinates its prevention research program with other federal research and services agencies through participation in formally organized interagency work groups and through the development of interagency Memorandums of Understanding (MOUs) that delineate areas where NIDA and other agencies jointly plan, fund, and coordinate prevention program development, delivery, and research implementation. NIDA participates in the NIH Prevention Coordinators Committee, which has as its mission collaborative planning and coordination of prevention research within the NIH. In addition, NIDA prevention staff participate in the Linkage group which consists of scientific prevention program directors in NIDA and CSAP. The linkage group serves as a vehicle of communication and joint planning in the area of drug abuse prevention. Further, NIDA supports interagency collaboration through the use of Memorandums of Understanding which serve as vehicles to support joint funding of drug prevention initiatives. NIDA has entered into an MOU with the Department of Education, Office of Drug Free Schools and Communities, by which the Department of Education transferred $500,000 to NIDA to support the dissemination of drug prevention research findings and methods to school systems throughout the country through training and technical assistance activities conducted by NIDA sponsored drug abuse prevention research centers.

Ms. Pelosi: What would your research suggest about ways to improve the Drug-Free School program?

Dr. Leshner: NIDA prevention research can assist the Drug-Free Schools program in a variety of ways. For example, research indicates that effective drug abuse prevention programs need to be risk focused and implemented with a high degree of fidelity to the program that was tested in the efficacy trial. To be successful drug prevention programs need to be theory-based, carefully designed to meet the needs of both general populations and high-risk youth, thoroughly tested, and fully implemented.

Ms. Lowey: You mentioned that young people's perceived risk of drug abuse has gone down in recent years and that phenomenon has contributed to rising rates of drug abuse. Does the Institute have data on why these perceptions have changed and are you supporting research into how these attitudes can be reversed?

Dr. Leshner: In 1992 the Monitoring The Future (MTF) drug abuse epidemiologic survey of a national representative sample of students in the eighth, tenth, and twelve grades reported, for the first time in over a decade, decreases in reported perceived risk of harm and disapproval of drug use. One year later, decreases in perceived risk and disapproval continued, and for the first time in over a decade increases in drug use (marijuana, stimulants, LSD, inhalants, and cigarettes) were reported. While specific data are currently not available to explain these reversals in trends, several hypothesis for these changes are currently under investigation. One hypothesis is that over the last four years national attention has shifted away from the drug problem to other issues. The shift of public attention away from drug abuse is seen in print and electronic media coverage of the news and interpersonal communication agendas. This lack of attention may be leading to a softening of formerly clear anti-drug use and abuse attitudes, perceptions, and social norms. A second, related hypothesis is that American family life over the past several years has experienced increased life stress, heightened parental frustration and anger, and interpersonal conflict between parents and children. Research by Conger, University of Iowa, suggests that economic stress leads to disruptions of skillful parenting practices and subsequently to adolescent adjustment problems in the home, school, and community and to increases in the use of illicit drugs. NIDA prevention research is assessing these hypotheses as well as others with specific research projects in progress and under development and through the development of two new grant program announcements. The first will stimulate research to assess the role of persuasive communication processes in drug use onset, progression, and discontinuation and to test the efficacy of media-based preventive interventions. The second grant program announcement will stimulate research to assess the role of family management and monitoring practices as a drug use protective (or risk factor) and to design and test theory-based family interventions.

Ms. Lowey: Your testimony mentioned a new treatment for heroin addiction, LAAM, 1-alpha-acetylmethadol, which appears to have several advantages over methadone. How much do you expect this new drug to be used?

Dr. Leshner: LAAM is currently undergoing re-scheduling and registration procedures in each of the 40 States which currently have methadone programs. This is a laborious task which often requires State administrative and/or legislative action. California, for example, anticipates it may take two years to finish this process. As LAAM is approved in each State, the sponsor will train each clinic in its use. Thus, the introduction of a narcotic treatment agonist medication such as LAAM is nowhere near as rapid as for other types of medicines.

LAAM was developed by NIDA to increase treatment options available to patients and clinicians. NIDA hopes that the addition of LAAM will allow the total number of U.S. opiate addicts treated with pharmacotherapy to increase from the current level of 110,000 to 150,000-200,000 rather than compete for the same patients currently taking methadone. For this to occur requires an expansion of treatment slots through State and Federal programs.

How much LAAM will be utilized remains to be seen over time. As with any new medication, it must first gain a reputation among clinic personnel and patients. Clearly, some patients will prefer LAAM while others prefer methadone. LAAM now offers a meaningful choice for patients and clinics. There is the possibility of some jurisdictions establishing LAAM only clinics, or some clinics expanding the number of addicts they can accommodate through the use of LAAM. The situation will vary from clinic to clinic.

Ms. Lowey: I was interested in your comments about the National AIDS Demonstration Research Program, which seeks to demonstrate outreach programs that can alter behaviors associated with the spread of AIDS. Recently, there have been reports about the ineffectiveness of outreach programs run here in Washington, needle-exchange program in particular. Are you familiar with the situation here in D.C. and what lessons do you draw from the results achieved here?

Dr. Leshner: Outreach programs have been found effective in many communities across the U.S. in reducing HIV risk behaviors of injecting drug users and in encouraging IDUs to enter drug abuse treatment. NIDA has funded two research studies in the District of Columbia that incorporate outreach activities:

Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research - The D.C. project was funded in August 1993. Research design and program implementation efforts have been developed and recruitment for HIV prevention trials were initiated in February 1994. Outreach efforts target out-of-treatment injection drug users, crack users, and their sexual partners, using a mobile van. Outreach workers distribute AIDS reduction literature focused on needle hygiene and high risk sexual practices and provide training in use of bleach and condoms. While only in operation a few months, these outreach efforts appear to be effective in recruiting and retaining clients in the program.

D.C. Initiative - Through November 1993 drug users were recruited to the D.C. Initiative by the outreach counselors of the Central Intake/Diagnostic Unit. The outreach counselors met with each potential patient individually to discuss treatment options and to confirm that each patient met the eligibility requirements for the study. Patients who did not meet the eligibility requirements were referred to the Central Intake Unit operated by the District of Columbia Alcohol and Drug Abuse Services Administration for treatment within one of their other, non-research programs.

NIDA was not involved in the development and implementation of a needle exchange program in D.C. (start-up, July 1992). We are, however, aware of difficulties the project has encountered in attracting and retaining participants. Basic principles of successful needle exchange that have emerged elsewhere indicate that to be effective a program must:

(1) contact addicts (a) who are not in treatment, (b) who might not be interested in entering treatment at this point, and c) who would respond negatively to coercive/intrusive attempts to change these attitudes;

(2) offer services that are easy to use in terms of location, hours of operation, numbers of needles/syringes that may be exchanged, equipment that is familiar/appropriate to existing drug use practices; and,

(3) offer services that are seen by the addicts as being safe to use from the point of view of preserving their confidentiality and not exposing them to the risk of arrest or criminal prosecution.

I understand that these principles were not incorporated in to the District of Columbia needle exchange program, which instead required that addicts be on a waiting list for treatment and providing considerable information about themselves as a condition for program entry.

Ms. Lowey: I am interested in your comments regarding the success of multifaceted treatment programs, particularly those which involved school-based interventions, parental involvement, and community action. Can you tell us more about the Institute's studies in this area?

Dr. Leshner: Drug abuse prevention research is an emerging scientific discipline that focuses upon testing under controlled conditions the efficacy and effectiveness of theory-based drug abuse prevention programs. Research has identified a number of temperament, familial, personality, peer-related and social/environmental conditions that may be precursors to the development of drug abuse, such as aggressive behavior, emotional distress, alienation and rebelliousness, poor social competence, anti-social behaviors, poor family management practices, low bonding to family, low commitment to school, and association with drug-using peers. Research indicates that focusing solely on the individual is an insufficient means of preventing drug use. Family, neighbors, peers, friends, teachers, and others in the social environment who encourage and reinforce positive behavior changes play a vital role in prevention. Prevention research assesses how to structure and strengthen social environments to promote positive, self-regulated health behavior. Meta-analyses of prevention research studies indicate that comprehensive strategies that use combinations of mass media, schools, family, peers, social networks, and health policies both to shape and reinforce self-regulated behavior change offer the best chance of preventing drug use behaviors for both general and high-risk populations.

Programs with supportive or enabling services and comprehensiveness of treatment appear to be more effective for some populations than a single intervention. Preliminary findings from the "Perinatal 20" portfolio suggest that for some women the availability of child care services, door-to-door transportation, coordinated scheduling across clinic appointments, and the availability of selected program components offered in neighborhood facilities and/or the home will increase the likelihood that these women will come to their scheduled appointments, and remain in treatment for a longer period of time. Comprehensiveness of prenatal treatment and drug abuse interventions have been shown to improve outcomes for both mother and newborns (e.g., increased birth weight). Moreover, methadone maintenance programs that include combinations of services are shown to produce superior results in terms of decreased drug use and criminality and other outcome measures than methadone maintenance with standard counseling only. Methadone maintenance with enhancements such as day treatment with social rehabilitation emphasis has been shown to result in reduced AIDS risk behaviors as well as reduced drug use compared to regular methadone maintenance. Adding a special vocational component to treatment has been shown to increase employment among clients in multiple studies. Adding special counseling focused on AIDS risk behaviors has been shown to increase motivation to stay in treatment.

Ms. Lowey: What do these findings imply for our national prevention and treatment strategies?

Dr. Leshner: This research suggests that multi-level prevention programs are needed across the developmental life span. "Universal prevention interventions" are needed to prevent drug use onset and progression for the general population. "Selective prevention interventions" are needed to meet the needs of sub-populations with one or more specific risk factors to drug onset. "Indicated prevention interventions" are needed for individuals who are already experimenting with drugs, but who as yet do not meet diagnostic criteria, such as DSM IIIR, for an addictive disorder.

Addressing needs more broadly has the potential to improve drug abuse treatment outcomes by improving the clients' overall well-being, and improving the motivation of the client to enter and become engaged in treatment. These preliminary findings indicate that a national strategy should include delineation of funding criteria that support and encourage activities and accomplishments related to cooperation and coordination among service providers associated with comprehensive drug abuse treatment program.

HISPANICS AND NIH

Mr. Serrano: Dr. Leshner, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions.

Mr. Serrano: First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Leshner: Efforts to recruit Hispanic researchers are considered critical to development of more effective interventions for Hispanics. NIDA staff have made extensive efforts to encourage Hispanic researchers to apply for research funding and for positions within the Institute. Recruitment efforts have included presentations by NIDA staff at scientific/professional meetings, such as the First Annual Conference on Psychology, Psychopharmacology, Substance Abuse, and Ethnicity in Los Angeles in October 1993 and the National Academy of Neuropsychologists in Phoenix in October 1993; multiple personal and telephone conferences with individual researchers to provide technical assistance; and active solicitation of applications from Hispanic scientists through correspondence and face to face meetings. Also, the Addiction Research Center (ARC) has developed a Minority Recruitment and Training Program which provides research experiences to minority students and faculty.

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Leshner: Last year, in 1993, NIDA spent approximately $25,000,000, or about 7 percent of the extramural research budget, on research specifically related to drug abuse in the Hispanic community.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Leshner: The following are a number of outreach activities geared to increase the participation of Hispanics in NIDA research:

--Several years ago NIDA developed a Special Populations Mentoring Program to provide grantsmanship training to underrepresented scholars interested in drug abuse research. The goal of the program is to increase the number of underrepresented scholars applying for and receiving NIDA support for research projects. Hispanic researchers are sought out to participate in this program, and they have participated each year.

--NIDA supports a Minority Institutions Research Development Program at the Hispanic Research Center, University of Texas at San

Antonio. Hispanic investigators are provided research experience and support and Hispanic students obtain research experiences as research assistants.

--We have a Hispanic Work Group to provide us recommendations on Hispanic health issues. Since 1989, NIDA has been working toward closer collaboration with the Hispanic drug abuse and HIV/AIDS community. In that year the Hispanic Research and Technology Transfer Work Group was created. It is composed of more than fifty Hispanic researchers, practitioners, and community leaders. The Work Group has developed and conducted five workshops for NIDA. The 1993 work group members developed papers on three policy issues. One paper focuses on the development of Hispanic researchers.

--For several years NIDA has provided support to the National Hispanic Youth Initiative in Health, Biomedical Research and Policy Development Program sponsored by the Interamerican College of Physicians and Surgeons. Hispanic high school youth from across the country are brought to Washington in the summer to participate in a program designed to prepare, motivate and encourage them to actively pursue careers in medicine, other health professions, and biomedical research.

--NIDA provides support to the Association of Minority Health Professions Schools' Annual Symposium on Career Opportunities in Biomedical and Public Health Sciences. About 1200 minority students, attended the symposium. The chief of the special populations office participated in the panel on careers at NIH, and the EEO officer attended and met students at the NIDA exhibit.

Mr. Serrano: Fourth, what is your institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Leshner: NIDA assures itself of access to minority populations, including Hispanics, by running clinical trials in major metropolitan areas. Sites have included Los Angeles, Miami, New York, Chicago, Philadelphia, Washington, D.C., and San Juan, Puerto Rico. NIDA also makes use of Department of Veterans Affairs Medical Centers and clinics where minorities, including Hispanics, are well represented.

The Cooperative Agreement for AIDS Community-Based Outreach Intervention Research Program conducts clinical trials to determine effectiveness of HIV risk-reduction interventions. Within the framework of this 22 site program, there are three investigators of Hispanic origin, and 24% of subjects are Hispanic, including 13% Puerto Rican and 9% Mexican Americans. Several sub-studies have been planned which also involve the recruitment of Hispanic subjects. These include:

--Women's Sexual Partners - HIV-related drug-using and sexual risk behaviors of female sexual partners of injection drug users is being investigated. The primary purpose of the study is to examine behavior change among female sexual partners and to determine whether certain characteristics of preventive interventions influence behavior change. A substantial proportion of the participants in this sub-study are expected to be Hispanic women.

--New York City/Puerto Rico Mobility, Risk Behavior, and Service Utilization - The New York and San Juan program sites are participating in a special study to examine mobility patterns of Puerto Rican drug users who travel between these two locations, HIV-related drug-using and sexual risk behaviors associated with this mobility, and several questions related to service utilization.

--HIV Drug and Sexual Risk Behavior Among Ethnic Minority Males - A cross site study involving at least five cooperative agreement sites will be conducted to gain a better understanding of the HIV and drug-related sexual risk behavior among African American and Hispanic males. Information from the sub-study will be used to develop more effective strategies to impact HIV sexual risk behavior.

--The WHEEL Project (Women Helping to Empower and Enhance Lives) involved multisite pilot testing of an HIV prevention model for women-at-risk who are sexual partners of injection drug users. More than 40% of the participants in this study are Hispanics.

--NIDA also convened a meeting of minority HIV-prevention investigators during the first week of May 1994 to discuss research themes relating to drug use and AIDS in ethnic minority communities. Major emphasis will be placed on examining new areas for investigation in Hispanic communities. Information obtained from this meeting is expected to increase program responsiveness to Hispanic issues and to identify potential Hispanic investigators.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Leshner: Of the 14 applications from principal investigators that were self-designated as Hispanic, NIDA made 6 awards, for a success rate of 43 percent, as compared with a 32 percent success rate for applicants who designated themselves as White.

INCREASED DRUG USE/DECREASED CONCERN ABOUT DRUG USE

Ms. DeLauro: In the past few weeks we have seen some very disturbing reports about increased drug use and a decrease in the concern Americans express about occasional drug use. To what factors do you attribute the recent jump in emergency admissions to hospitals for drug treatment -- a 9 percent increase nationwide in the first six months of 1993?

Dr. Leshner: The number of emergency room episodes, particularly the number of heroin-related emergencies have increased steadily since the second half of 1990. The increase in heroin-related mentions is especially noteworthy for persons visiting the emergency room because of an overdose, adverse health conditions caused by habitual drug use, or an effort to seek detoxification (collectively accounting for over 70 percent of all heroin mentions). Even with the economy moving out of a period of decline, over 37 million persons still do not have health insurance, and many may have to depend on the hospital emergency room as their sole source of primary and urgent care. The increase may also be related to the change in the type of services offered by hospitals. For example, in the 1980s more detoxification units began to appear in the DAWN hospital sample as the demand for this type of service increased.

Ms. DeLauro: The increase was particularly striking for heroin-related cases. Do you have any thoughts on why this is so?

Dr. Leshner: According to the Department of Justice, purity of an ounce of heroin from 1990 to 1993 has risen sharply (from 34 percent to 65 percent) while street prices have remained consistently low over the same period of time.

Ms. DeLauro: A survey released in the past few weeks found that large numbers of Americans do not think using cocaine, marijuana and other drugs occasionally is a great threat to their health. Only 54 percent of youths from 12 to 17 believe using cocaine once or twice presents a great risk, and only half of them think smoking a pack or more of cigarettes daily is a great health danger. Another survey found one-quarter of all 12th graders were smoking marijuana compared to one-fifth two years earlier. Can you share any insight with the Committee as to why we are seeing this shift in attitude about drugs -- as well as use, particularly among the young -- which is a reversal of the generally downward trend we saw in the late 1980s?

Dr. Leshner: One hypothesis is that in the 1990s, national attention has shifted away from the drug problem to other issues. According to this hypotheses, the shift of public attention away from drug abuse is constantly being seen in print and electronic media and, as a result, has softened the anti-drug messages and the perceptions and attitudes about the harmfulness of drugs. A second related hypothesis is that many families have experienced increased stress, heightened parental frustration and anger, and interpersonal conflict between parents and children. Research has shown that economic stress can lead to disruptions of skillful parenting practices and subsequently to adolescent adjustment problems in the home, school, and community and to the increases in the use of illicit drugs. In addition, some of the drug use patterns appear to be reminiscent of what was popular in the early days of the 1970s drug epidemic, so adolescents may need to learn the hard way the same lessons that were learned 15 to 20 years ago.

Ms. DeLauro: I see from your testimony that you will be launching a Behavioral Therapies Development Program. What level of funding will be devoted to that Program?

Dr. Leshner: Current plans call for an initial $3,000,000 investment in the Behavioral Therapies Development Program for FY 1994, with a further expansion to $4,500,000 under the FY 1995 request.

Ms. DeLauro: How much overall funding does NIDA devote to research on the behavioral and motivational aspects of drug abuse? Can you provide for the Committee that level of funding for the past 3 fiscal years, and what you plan to spend in FY 1995?

Dr. Leshner: The following is the budget for research on behavioral aspects of drug abuse:

1991 -- $156,100,000
1992 -- $168,472,000
1993 -- $173,500,000
1994 -- $185,800,000
1995 -- $192,400,000

Ms. DeLauro: How will you work with the Office of Behavioral and Social Sciences, once that office is up and running -- will research funded through that Office supplement, rather than replace, behavioral research you support?

Dr. Leshner: It is our understanding that the Office of Behavioral and Social Sciences Research will primarily coordinate and stimulate behavioral research across the NIH institutes. As we understand the organization of the office, it will consist of a small core staff who will serve to assure communications and information exchange, identify areas for collaboration, and areas where additional research is needed, rather than as an independent funding source.

DRUG ABUSE IN WOMEN

Ms. DeLauro: Are there differences between men and women in the rate of their abuse of various drugs?

Dr. Leshner: In general, studies of deviant and antisocial behaviors have shown that prevalence rates are significantly lower for girls and women than for boys and men. However, these observations are changing, and certainly for substance abuse, women are beginning to show increasing rates of involvement. Women's substance abusing behaviors also have been of a more traditional nature--using alcohol or prescription medications--thus avoiding the criminal distribution networks. And even when women do use more stigmatized drugs such as marijuana, cocaine and heroin, they generally have received these drugs through their male significant other. Recent trends in our national and locally-based epidemiologic studies indicate that women are using more tobacco and marijuana and, in some cities, more women are involved at high levels in the trafficking of drugs. We are not sure why these changes are taking place but there are several hypotheses related to the changing role of women in this society and to the multiple generations of drug use in families.

Ms. DeLauro: Are you looking into why this may be so, both in terms of possible physiological differences, as well as behavioral factors?

Dr. Leshner: Preliminary data suggest that women may more rapidly proceed to addiction after casual drug use than men, and that effects of marijuana and alcohol use in women are associated with the menstrual cycle. These data raise questions about possible fundamental gender differences in the reinforcing and stimulus properties of abused drugs. Such studies have been reported in animal studies with rodents. On several measures of stimulant-induced activity, females exhibit more responsiveness than males, and this responsiveness varies with the estrus cycle. Gender differences in self-administration of cocaine have been reported. When cocaine infusions were made contingent upon increasingly higher numbers of bar presses, female rats made substantially more presses than males and their level of cocaine self-administration varied as a function of the estrus cycle.

The pathways to drug abuse for females is slightly different than it is for males; smoking of tobacco is more highly associated with illicit drug use. One interesting finding that requires further investigation is the association between smoking in children with smoking in mothers, which is significantly stronger than with smoking in fathers. In utero exposure to smoking has a differential impact on girls and boys, with girls more likely to be affected. This association is particularly strong between mothers and daughters. Indeed, if more women are smoking, if the association is a valid link between the onset of smoking in children, and if smoking in children is linked to the onset of illicit drug use, we may be seeing additional drug use problems in the future.

The risk factor that is becoming a very significant one in our research is victimization under the age of 18, especially involving rape or sexual assault under the age of 11. A survey of a nationally representative sample of women found that 80 percent who had sought or received drug abuse treatment were the victims of early trauma. Crime victims meeting the criteria for Post Traumatic Stress Disorder were 9.7 times more likely to have major alcohol problems and 17 times more likely to have major drug abuse problems than nonvictims. Data from the National Comorbidity Survey, suggest a path for comorbidity is a neurobehaviorally vulnerable child of a mother who meets the criteria for an anxiety or depressive disorder who is also exposed to environmental trauma.

There is a great deal that we do not know about drug using patterns among females in the United States. This is particularly true for women across ethnic groups. We know that metabolites of illicit drugs are differentially stored and recirculated based on gender, age and physiologic reactions to stress. Historically, as drug abuse has been considered more a male disorder, the focus of many of the studies on the consequences of drug abuse have included men. More intensive studies of girls and women need to be developed. Because of the national interest in children, more recent studies of women focused on women not as women per se but as mothers. For this reason, women have been underrepresented in the National agenda for drug abuse activities, including research NIDA is rectifying that situation through the announcement, PA 93-059, "Etiology, Consequences and Behavioral Pharmacology of Female Drug Abuse" and through a technical review planned for June 1994, "Methodological Issues: Etiology and Consequences of Drug Abuse Among Women," and a conference on women's health scheduled for September 1994.

SERVICES RESEARCH PROGRAM

Ms. DeLauro: I am encouraged by the statement in your testimony that "NIDA views research on drug abuse treatment and prevention services, the linkage between drug abuse and the primary health care system, and HIV/AIDS prevention services research as major components of our research program." I believe such research is critical. We must address a person's entire needs -- for example, day care for drug addicted mothers while they are in treatment -- if we are to be truly successful. I understand NIDA is preparing a 5-year plan for drug abuse health services research. Can you tell the Committee what research will be incorporated into this plan?

Dr. Leshner: Last year, NIDA prepared and forwarded to the Congress a report which details the extensive services research portfolio of the Institute. Health services research at NIDA involves studies on the organization, financing, and management of drug abuse and other health services and their impact on the quality, cost, access to and outcomes of care. The NIDA health services research program focuses on health services issues as the relate to drug abuse treatment and prevention, prevention of HIV transmission and other adverse medical consequence associated with drug abuse, and primary care service delivery intended to impact drug abusers' concomitant medical disorders.

Ms. DeLauro: When do you expect that plan to be completed? Will your future budget requests anticipate adequate funding for research outlined by the plan?

Dr. Leshner: NIDA has appointed a Program Management Committee to coordinate health services research across the various NIDA divisions and to interact with services research components outside the Institute. The committee held two meetings with outside experts and consultants working in the drug abuse field to obtain their assessment and recommendations for research needs and opportunities in this area. The FY 1996 budget will reflect the product of this planning effort. NIDA is committed to expanding the health services research portfolio of the Institute, moving effective drug abuse prevention and treatment from the university clinic into real world settings. The FY 1995 request anticipates that fully 15% of the

Institute's appropriation will be directed to health services research, as does the Institute's professional judgement budget.

Ms. DeLauro: What level of resources is devoted to health services research in the current fiscal year? How does that compare to FY '93, and what do you plan to spend in FY '95?

Dr. Leshner: Last year, in 1993, NIDA spent $57,700,000 on health services research. This amount will increase to $63,800,000 in FY 1994, an increase of +10.5%, and then by another 4.4% to $66,600,000 in FY 1995.

NATIONAL INSTITUTE OF NURSING RESEARCH

SUCCESS RATES

Mr. Smith: Your Institute's success rate continues to be one of the lowest at NIH, despite the fact that your total new grants are projected to increase in 1995. Are you a victim of your own success, generating more interest in the field than you can satisfy, given existing budget constraints?

Dr. Hinshaw: The establishment of a new research component at the NIH always generates additional interest in the field and increased high-quality applications for research project grants--the National Institute of Nursing Research is no exception. After being established by Congress as an organizational component at the NIH in 1986, the nursing community has responded enthusiastically with many high caliber applications, and the field has indeed grown as one would naturally expect. The establishment of nursing research at the NIH was shortly followed by very difficult economic times and increased competition for scarce resources. The pattern of funding for most newly created Institutes is to receive much larger than average increases in the early developmental years. Such usual funding growth curves parallel the growth of research grant applications. After a few years, the numbers of applications stabilize, and percentage increases allow success rates to remain fairly constant. The situation for the NINR is that smaller percentage increases were instituted before the stabilization of the submission rate, thus the NINR is consistently nearly 15 points below the average NIH success rate. When percentage increases are applied to a very small base, the gap continues to slowly widen.

RESEARCH GRANTS VS. RESEARCH TRAINING

Mr. Smith: Have you considered transferring funds from research training to research grants, since you already have more researchers in the field than you can support?

Dr. Hinshaw: The NINR has in the past transferred resources from the research training mechanism into research grants. However, while it may appear that there are more researchers in the field than can actually be supported, in 1992, only 0.5 percent of working registered nurses held doctoral degrees. Additionally, each year there are more schools that qualify for institutional training awards to support predoctoral and postdoctoral trainees, thus the need for research training opportunities is likely to increase in the future. With health care reform, there will be even more need for well-trained nurse scientists in the field. Furthermore, the 1985 report from the National Academy of Sciences regarding the need for biomedical and behavioral scientists recommended that the numbers of nurse researchers be substantially increased to a total of 320 by 1991. To date, the NINR has been unable to meet the 1985 recommendations--our FY 1995 estimate is 208 full-time training positions. In addition, the 1985 report was recently updated, and the draft recommendations have recently been forwarded to ICD

Directors. The new report recommends a level for NINR of 500 trainees.

LONG-TERM STRATEGIC PLAN

Mr. Smith: Where do you stand with regard to implementing your long-term strategic plan? Are the priorities you have identified for 1995 contained in your plan?

Dr. Hinshaw: The National Nursing Research Agenda (NNRA), a component of NINR's long-term strategic plan, has been highly successful in promoting depth in the knowledge base for nursing practice. For example, through the implementation of the first NNRA priority--Low Birth Weight: Mothers and Infants--the issues surrounding the prevention of low birth weight and its impact on infants and their families are being identified and investigated by NINR grantees and through collaborative programs with other NIH ICDs.

In another NNRA priority area--Long-Term Care for Older Adults--the research program has been expanded to examine the impact of environmental and organizational factors on the quality of care in nursing homes. This initiative builds on previous studies to develop approaches to clinical management, strategies to promote self-care, and interventions for clinical problems such as urinary incontinence.

Of the four research priorities identified for FY 1995, three are specifically designated as high priority in the NNRA:

(1) Nursing Interventions: Symptom Management in HIV Infection. This extramural initiative is a direct expansion of studies carried out by NINR's intramural program to develop interventions to alleviate symptoms, such as fatigue and muscle wasting, and improve the quality of life for AIDS patients.

(2) Primary Prevention of Risk-Factor Development in Younger Children. NINR will expand research based on findings from prior studies of older children and adolescents to the younger age group in order to facilitate the adoption of healthy behaviors by children and their parents, e.g., controlling weight, maintaining low-fat diets, exercising, and avoiding risky behaviors such as smoking and drugs.

(3) Community-Based Culturally Relevant Care. NINR will undertake a program of studies to stimulate the development of primary health-care interventions for vulnerable and underserved populations in inner city, urban, and rural areas.

The fourth research priority for 1995, Research on Health in Midlife Women, has resulted from NINR's strong support for the NIH initiative in women's health research and the nursing research focus on symptom management. As directed by Congress, NINR will continue to build on its substantial base of research on women's health to identify and study menopausal symptoms and syndromes and develop interventions that alleviate or prevent the accompanying diseases and disorders experienced by midlife women. In addition, NINR will continue its studies on women with breast cancer and the management of symptoms associated with breast cancer treatment.

The remaining NNRA priorities will be phased in at annual intervals. Several of the research emphases for these priorities will build on research in areas of previous NINR-supported research, e.g., HIV infection, cognitive impairment, and chronic illness.

PATIENT OUTCOMES RESEARCH

Mr. Smith: Why are you increasing your efforts in patient outcomes research, given that there is already a Federal agency--the Agency for Health Care Policy and Research--that is tasked with this type of research?

Dr. Hinshaw: NINR began a focus on examining the effectiveness of nursing practice and its effects on clinical outcomes after consultation with the scientific community. These consultants indicated that nursing was not included in the existing patient outcomes research efforts and that there were scientific issues of how to best measure the effectiveness of nursing practices that were different from the measurement issues for medical practice. Based on the recommendation of these consultants, NINR convened a state of the science conference specifically focused on the scientific issues in examining the effectiveness of nursing care and its influence on clinical outcomes.

Staff from the Agency for Health Care Policy and Research (AHCPR) Center for Medical Effectiveness Research were involved in the planning and conduct of the conference. Recommendations from the conference participants which included public participation were made to both NINR and AHCPR. Staff from both agencies have held joint planning discussions since the conference. NINR funds research that focuses directly on clinical nursing care, the relationship of nursing interventions to patient outcomes, and the basic science mechanisms for explaining these relationships. To date, NINR has funded one initiative on measurement issues in nursing effectiveness and outcomes research. In FY 1995, NINR will initiate a small grants program targeted to nursing effectiveness and outcomes research to stimulate small scale studies and supplements to existing patient outcomes research.

RESEARCH CENTERS

Mr. Smith: Identify the number, type, and subject matter of research centers supported in 1994.

Dr. Hinshaw: In FY 1994, the NINR will fund two noncompeting exploratory research centers which are part of NINR's symptom management research program. The subject areas are Pain, Fatigue, and Sleep Alterations in Cancer Patients, and Biobehavioral Studies of Fatigue Management. Additionally, a Request for Applications (RFA) has been published for research center core grants. It is anticipated that five grants will be funded by the end of the fiscal year. These research center core grants will focus on important scientific areas of nursing research including women's health and symptom management in chronic illnesses, such as Alzheimer's disease.

HEALTH CARE REFORM

Mr. Stokes: As the nation approaches health care reform, what can nursing research do to help strengthen and improve the Nation's health care delivery system?

Dr. Hinshaw: One of the most striking challenges of health care reform is balancing high quality health care with the cost of providing health care. There are many ways that nursing research can address this problem. Some current NINR-sponsored research projects have preliminary findings that include important cost implications. For example, one study is comparing the care of low-risk women before, during, and after childbirth by certified nurse-midwives and by physicians in terms of quality of care and cost savings. Patients of the nurse-midwives showed lower maternal morbidity and higher satisfaction with care, and total charges were almost 10 percent lower for the mothers (baby care charges were the same). Another study investigated the impact on health care quality and cost of clinical nurse specialists providing transitional home follow-up care when patients are discharged from the hospital early. Cost savings were 29 percent for women having cesarean births; 38 percent for new mothers with diabetes, and 6 percent for women with hysterectomies. In all these populations, the quality of care was maintained or enhanced.

In addition, nursing research may inform other aspects of change that will be vitally needed to implement whatever health care reform proposal is enacted. For example, new ways to organize acute hospital care will continue to be needed, particularly testing of clinical management strategies designed to maintain quality while achieving cost savings. NINR is currently funding such a study which, if preliminary findings are substantiated, has the potential of reducing the hospital costs for patients needing intensive care over a long time period. These chronically critically ill patients tend to be very costly to individual hospitals and thus to the Nation's health care system. Among these are examinations of strategies to provide health care in the community, especially to vulnerable and underserved populations residing in inner cities and rural areas. NINR will target research on community-based health care models as a priority in FY 1995. This initiative will focus on increasing our understanding of the influence of cultural and behavioral factors on the effectiveness and outcomes of health care, and our capability of providing culturally sensitive and acceptable clinical treatments and interventions. The emphasis will be on vulnerable and underserved populations, such as minority groups in inner cities and rural areas.

HEALTH PROMOTION AND DISEASE PREVENTION

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your institute?

Dr. Hinshaw: Health promotion and disease prevention have been major thrusts of nursing practice, nursing research and the NINR. NINR invests approximately 45 percent of the extramural research funds in health promotion/disease prevention research with particular emphases on child and adolescent health, reproductive and women's health, the health and well-being of older people, and chronic, recurrent health problems. Studies are investigating innovative and culturally sensitive methods to reduce the frequency of low birth weight infants, to reduce cardiovascular risk factors in children (improved diet and frequency of exercise), to increase the frequency of screening for common age-related cancers and to promote health enhancing behaviors such as smoking cessation and stress management.

During the past two decades, the relationship of health and behavior has received increasing attention, particularly as research has linked the results of high-risk lifestyles and health compromising behaviors with the prevalence of health problems and disease, poor quality of life in later years, and the accompanying increasing costs in health care with an aging population. While considerable information regarding health behaviors in adulthood has been generated, data are lacking on the acquisition and maintenance of health behaviors in young children. It is clear from research to date that risk factors for many chronic diseases develop early in childhood. Further, although pre-adolescence and adolescence are times when children develop risky behaviors at an accelerated rate, there is little understanding about how individuals are shaped by their early childhood environments in ways that prevent or promote the adoption of risk-taking versus health-promoting behaviors.

In FY 1995, NINR will launch an initiative on primary prevention of risk factor development in younger children. Questions of interest include (1) the interaction of environmental influences (both social and physical) with biological and cognitive characteristics that predispose young children toward activity and dietary patterns, (2) the development of health-enhancing resiliency and positive coping patterns among young children experiencing adverse circumstances, and (3) the role of parents and family in the acquisition of health behaviors in young children from diverse populations.

A second prevention initiative for FY 1995 concerns the normal processes and health of midlife women. There a number of symptoms and/or syndromes that occur in some midlife women that are poorly defined and understood. They include functional disorders involving musculoskeletal symptoms, gastrointestinal symptoms, fatigue, sleep disturbance, weight gain, vasomotor instability (hot flashes), depression and mood swings, changes in cognition and perception, and memory alterations. The absence of a clear pathology, extensive symptom overlap, and no well-defined treatments are common features of these disorders. These symptoms, which may persist over many years, are often a major reason for women to seek medical care, lose time from work, and experience a decrease in health-related quality of life. Lack of specific pathology often leads to labeling these syndromes as functional or psychosomatic and to treatment with nonspecific pharmacologic agents (e.g., sedative and tranquilizers or surgery. The accompany pattern of side effects from these treatment sometimes further debilitate the patient. In FY 1995, NINR will issue a Program Announcement on the health of midlife women, calling for research to better understand the relationship between menopausal symptoms and the biobehavioral mechanisms responsible for their alleviation or exacerbation. The development of better treatments and methods to prevent midlife symptoms rests on understanding their origin and relationships.

AGING RESEARCH

Mr. Stokes: The elderly is one of the fastest growing segments of America's population. What advances in nursing research over the last five years have helped to prolong their independence? What opportunities and advances are on the horizon?

Dr. Hinshaw: Improving the health and quality of life of older adults is a major goal of the PHS Healthy People 2000. The NINR has addressed a number of research issues of great concern to scientists and to older Americans. These areas include the interruption and management of the disruptive and distressing behavioral symptoms occurring in Alzheimer's disease, and the development of protective garments to reduce the likelihood of a hip fracture in the event of a fall.

Most care for Alzheimer's disease patients is provided by family members and by nurses and nurses's aides in long term care facilities. The non-cognitive behavioral symptoms, such as wandering, aggression, toileting and dressing difficulties, screaming and other inappropriate vocalizations are very troublesome and difficult to manage. NINR and NIA are supporting 23 developmental studies in an effort to design effective, inexpensive and dignified procedures for interrupting and managing these symptoms to improve the quality of life of the patients and the care-providers. The outcomes of these developmental studies will lead us to full-scale clinical trials of interventions for behavioral symptom management in Alzheimer's disease. Ultimately, it is expected that these studies will fundamentally change the way in which care is provided for demented people. The prevention of or successful management of the secondary symptoms of Alzheimer's disease has enormous implications for improving the quality of life of the patients and the caregivers as well as reducing the cost of care in long-term care facilities.

Hip fractures and their consequences are devastating events and are greatly feared by older people who often unnecessarily limit activities to reduce the risk of a fall and possible fracture. NINR has supported a major investigation, in collaboration with NIA, to develop a passive intervention, the wearing of hip pad, to reduce the risk of a fracture of the hip after falling. The specially designed hip pads and garments have gone through extensive testing to ensure that older people will actually wear them. The compliance rate has now gone up to 75-80 percent of waking hours--which means simply that people in the study are protected by the pads more than 3/4 of the time. The prevention of hip fractures is vital for maintaining independence, maximizing the quality of life and reducing the almost 24 percent one-year post-fracture death rate.

Important opportunities for additional research exist in management of Alzheimer's disease symptoms and in the prevention of falls and hip fractures. Other nursing research questions of great important to the health of older people include how to provide services in the home or community setting which are culturally appropriate and maintain the best possible outcome.

COLLABORATIVE RESEARCH INITIATIVES

Mr. Stokes: Can you describe for us some of the most significant collaborative research initiatives underway between the Nursing Institute and other institutes, centers and divisions of the NIH? What have been some of the major results of those collaborative efforts?

Dr. Hinshaw: Nursing research aims to provide better care and treatment to the patient, as well as to promote health and prevent disease. It does this by translating results from basic science to clinical applications that can be used by the nurse at the bedside to deliver better care to the patient. In this manner, nursing research is ideally suited to cut across all disciplines of medicine, and opens the door for collaborative research efforts with many of the categorical institutes at the NIH. For example, NINR has had substantial collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Aging (NIA), and the National Heart, Lung, and Blood Institute (NHLBI). Of particular note are collaborative studies involving our intramural scientists. For example, on- going NINR studies which interface with NIAID have focused on problems occurring in HIV Disease as a chronic illness: nutritional changes as the disease progresses, muscle wasting during the course of drug therapies, and the quality of life of these persons as they learn to live with the detrimental effects of the disease. All subjects in these studies are currently subjects in NIAID clinical research protocols that are investigating the effects of various combinations of drugs for the treatment of HIV Disease. The research provides NINR access to a sensitive group of subjects who might not be easily assessable in the community. The NINR studies enable the subjects to participate in protocols that expand the investigation of toxic effects of the drug treatments to the management of these side effects and identification of other interventions to improve the quality of their lives. Nursing research studies are crucial to the well-being and independence of individuals and provide important complementary information to traditional biomedical research.

Cooperative endeavors with NIA have occurred via the intramural program at the Gerontology Research Center in Baltimore, where an NINR scientist is based. The focus of the nursing research is on two major issues for older women who are hospitalized or in nursing homes: urinary incontinence and hip fractures. Both of these costly health problems result in increased morbidity: complications, such as decreased functional ability and independence, prolonged hospitalizations, and caregiver burden.

Collegial research relationships with NHLBI and NIA were instituted when an NINR scientist jointed the Honolulu Heart Program (HHP) in Hawaii. The HHP began as an epidemiologic study of risk factors for heart disease and stroke. NIA has instituted a study of dementia in the elderly Japanese American male cohort, and NINR is conducting a longitudinal study of caregiving and quality of life in caregivers of men with dementia. The NINR scientist has been able to expand the study to include the wives and daughters of the Japanese American men, as prior to NINR involvement, the investigations only involved men. Participation in the HHP allows NINR access to the largest, longest living cohort of minority persons, a population that would not be accessible otherwise.

Extramural collaborative endeavors include studies with the National Cancer Institute (NCI) on breast cancer treatment in older women and psychosocial interventions in cancer, and a joint effort with the NIA dealing with the management and symptoms of Alzheimer's disease. These studies are showing potential for managing behaviors such as pacing, aggression, sleep disturbances, and communication problems.

MINORITY PARTICIPATION IN NURSING RESEARCH

Mr. Stokes: What initiatives are underway to increase minority participation in nursing research?

Dr. Hinshaw: NINR actively supports individuals from minority groups interested in research. Our goal has been to facilitate our currently funded investigators in seeking support for minority individuals who have an interest or even a budding interest in a science career. We have provided support for research experiences for undergraduate, master's and doctoral level minority students in nursing and related scientific disciplines, and for minority investigators who wish to become more research intensive. Furthermore, the NINR enthusiastically supports the NIH Research Supplements for Underrepresented Minorities initiative and has virtually led the NIH with number and dollars awarded as a percentage of eligible research grants. In addition, NINR participates in meetings with members of the National Black Nurses Faculty Association and the National Hispanic Nurses Association to discuss ways to stimulate increased activity of faculty and students in nursing research. NINR has also provided workshops to provide grants technical assistance that have included minority individuals interested in research grant support.

OUTREACH ACTIVITIES

Mr. Stokes: To what extent is the institute involved in the conduct of outreach activities, describe your target audience, and the purpose of the outreach.

Dr. Hinshaw: NINR has been involved in outreach activities with organizations that represent minority nurses who are interested in research. These activities have included meetings with these organizations on a regular basis. NINR has led the development of the National Nursing Research Roundtable, a group of nursing organizations interested in fostering nursing research, that meets annually. The purpose of these meetings is to discuss ways NINR can support the development of nurse scientists, especially those from minority groups. Each of these organizations has been active in assisting NINR to identify fruitful ways to accomplish this. NINR has also conducted regional development workshops for faculty and other individuals interested in research.

ADVANCES IN RESEARCH

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your institute?

Dr. Hinshaw: The pipeline needed to maintain and eventually hasten the progress of nursing research is short and of much concern. Nursing research is a relatively new and growing area with a great deal to contribute to the scientific questions underpinning health care reform. Nursing research also addresses the management of the symptoms of acute and chronic illness, optimum and culturally relevant strategies for health promotion, and the development and testing of community based models of nursing care. The need for well-trained nurse scientists in a number of areas, including advanced technologies, is critical.

The components required to develop a cadre of well-trained scientists are many. One of the most important components, however, is a research intensive environment. The optimum environment is one in which a number of projects are underway, where the facilities and equipment are adequate, and where senior, experienced investigators are available and accessible to serve as mentors and role-models for junior scientists. NINR has been concerned about and has worked to develop such research intensive environments for nurse scientists.

The last report on the supply of nurse investigators was produced in 1985 as part of the National Academy of Sciences report on manpower needs in the biomedical and behavioral sciences. That report indicated that the number of nurse investigators in training at both the pre- and post-doctoral levels should be substantially increased. An updated report by the Institute of Medicine, National Academy of Sciences, is due to be released shortly. It is expected that it will again be noted that the supply of nurse investigators is inadequate.

NINR has been very concerned about the number of nurse investigators in training. The multiple demands for available resources have made it impossible to meet the projections of the 1985 report. The gap between the supply and the need is simply widening with time. Additional attention must be paid to the development of and stable support of creative and stimulating research training environments.

MINORITY RESEARCH AND TRAINING

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your institute?

Dr. Hinshaw: In FY 1993, NINR convened the Task Force on Minority Health and Recruitment of Minority Investigators for the third time. This group reviewed the current status of nursing research with minority populations and the current status of initiatives to increase the numbers of nurse scientists from minority populations. The Task Force directed its recommendations to NINR and educational institutions preparing nurse researchers. These recommendations included: reconsideration and reevaluation of the depth of institutional commitment to research in light of the resources available; development of the institutional infrastructure to support research; provision of mid-career programs to assist scientists to move into newly developing areas of science; development of procedures for identifying and reaching non-university-based minority scientists, especially in rural areas; and initiation of plans to have cultural groups represented in all NINR research initiatives and long range planning activities.

NINR has supported several investigators whose research is substantially focused on minority populations at high risk for specific health problems. Among these are studies of nursing interventions targeted to reducing risk of high cholesterol among rural minorities, of cancer among southern African American residents, of HIV infection among urban African American women, and diabetes among mid-western Native Americans. Some NINR supported investigators are exploring why there are differences among minority groups in use of health care services. Among these are studies of differences in the use of long-term care services, including nursing homes, home care and respite care, among urban and rural African American and White populations; and the barriers to appropriate breast cancer treatment for urban older Hispanic women who have a history of receiving suboptimal care.

In FY 1995, NINR will begin an initiative on community-based health care models for vulnerable and underserved minorities and residents of rural and inner city areas. This initiative will focus on models of primary health care during the first year and supportive restorative care during the second year.

MINORITY RESEARCH

Mr. Stokes: Please describe the measures your institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Hinshaw: NINR uses our minority task force to advise us on issues related to research and training needs for health problems that disproportionately affect minority individuals. Nursing has long recognized minority groups as one of the vulnerable populations that need particular health care attention, and program staff are well versed in the critical health problems. We have participated in a number of initiatives and fund studies which address diseases and disorders such as diabetes in Hispanic, American Indian, and African-American populations and low birth weight infants in African-American and Hawaiian women. In addition we fund studies addressing long-term care for older minority persons with chronic illnesses. These projects address the numerous cultural, educational, geographic, and economic factors that affect these minority persons. In all initiatives, such as a current one on the management of acute pain symptoms, we emphasize the need to pay particular attention to the understudied minority groups.

PRIORITIES IN MINORITY RESEARCH AND TRAINING

Mr. Stokes: How does your institute identify its priorities for investments in minority research and research training?

Dr. Hinshaw: NINR principally identifies the priorities for its research through the development of the National Nursing Research Agenda, a process that includes the scientific community in decision-making and is guided by the National Advisory Council on Nursing Research. Through this process a conference of investigators was recently held to develop the priorities for the second stage of the Agenda. The first new priority is on community-based health care models for vulnerable and underserved populations that reside in rural and urban inner city areas. Minority populations are being directly considered by the panel of scientific experts reviewing the state of the science for this priority and will be specifically targeted through the resulting research initiatives that will be funded in FY 1995.

MINORITY SUPPLEMENTS

Mr. Stokes: I understand that a number of the institutes make minority supplement awards, and that these awards hope to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Hinshaw: The NINR enthusiastically supports the NIH Research Supplements for Underrepresented Minorities initiative and has virtually led the NIH with number and dollars awarded as a percentage of eligible research grants. Since the inception of this program in 1990, 32 individuals have been supported at the undergraduate (7), graduate research assistant (14), postdoctoral

(1), and investigator levels (10). Only those at the postdoctoral and investigator levels apply for research project grants, and at this time, five of the ten investigators and the post-doctorate are still receiving minority supplemental awards. Thus, due to the relative newness of this program, only four investigators have submitted applications to NIH as principle investigators. Three of these applications are pending review, and one received a score too low for funding.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES (HBCU)

Mr. Stokes: What are some of the major initiatives underway at your institute to increase the participation of historically black colleges and universities (HBCU) in biomedical research?

Dr. Hinshaw: NINR has had a strong commitment to increasing opportunities for minority individuals to enter and progress in a scientific career. NINR staff have worked with faculty at Howard University's College of Nursing, and they have provided consultation to other faculty of historically Black colleges and universities. There have been some limitations in doing this, however, because such schools do not have doctoral program to prepare nurse scientists and few have masters programs. Research intensive faculty usually work in schools with graduate programs. As many of the historically Black schools do not have them, faculty in these schools may lack the infrastructure necessary to support their research efforts.

MINORITY EMPLOYEES

Mr. Stokes: How many GS-15 and above positions are there in your institute? How many employees in your institute are in GS-15 and above positions? In your institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze? If so, what was the response? If the freeze were lifted, how would it help the EEO problem in your institute?

Dr. Hinshaw: The NINR has 9 positions at the level of GS-15 and above; currently 8 of these positions are filled. While there are no African-American employees at the level of GS-15 and above at this time, the Institute does have a Hispanic male at this level. The NINR is proud of its record of hiring minority employees. For example, of the 15 positions at the GS-14 level and above, 27 percent are minorities; and for the Institute as a whole, more than 25 percent are minorities. The NINR has no pending cases for exception to the freeze on appointments and promotions to the level GS-15 and above.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES (HBCU)

Mr. Stokes: What is the present level of support provided to minority institutions by your institute?

Dr. Hinshaw: At the current time, NINR is not supporting any research projects at minority institutions. This is a direct result of the fact that there are no doctoral nursing programs in minority institutions with research intensive environments and thus limited numbers of trained minority investigators. To remedy this situation, NINR has, since its establishment at NIH in 1986, placed major emphasis on the provision of research training opportunities for minority individuals. The Institute has enthusiastically endorsed the NIH minority research supplement program to assist our minority colleagues to develop as independent, competitive investigators in nursing research. From the inception of this program in 1990, NINR has led the NIH each year with the highest dollar amount for minority supplements as a percentage of total expenditures for eligible research grants.

In further efforts to encourage minority individuals to pursue research careers, the NINR is one of only three ICDs at NIH to initiate its own program of minority supplements to institutional NRSA training grants. This program has also become highly successful.

NINR is involved in other activities to foster research and research training opportunities for minority investigators and to target minority health research issues. A meeting of the NINR Ad Hoc Task force on Minority Health Research in FY 1993 resulted in recommendations concerning research training and career development needs for minority investigators and nursing research needs in minority populations. NINR also participated in the Second Minority Invitational Congress held in the summer of 1993 to facilitate leadership among minority nurses of all backgrounds.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES (HBCU)

Mr. Stokes: Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the institute's programs and activities.

Dr. Hinshaw: NINR is committed to increasing the opportunities for minority individuals in science. NINR staff will provide and has provided consultation and technical assistance to faculty of these schools. The schools however need to develop a cadre of faculty who can work together and provide each other with stimulus. One means to accomplishing this is to open graduate programs in those historically Black colleges and universities that have other existing graduate programs on which to build a graduate program in nursing science. This is beyond the purview of NINR, but NINR staff can provide consultation to faculties that wish to increase their research intensity.

UNDERREPRESENTED MINORITIES IN BIOMEDICAL RESEARCH AND TRAINING

Mr. Stokes: Explain the proposed funding for the programs of your institute designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Hinshaw: NINR has initiated supplements to institutional training grants for minority individuals who wish to begin a career in science. These supplements can be for undergraduate, master's and doctoral level students and for postdoctoral trainees. These supplements have been sought after when such minority individuals are available and interested. In addition, NINR has led other NIH institutes in supporting supplements to ongoing research grants to provide research experiences to minority individuals interested in learning about science.

BREAST CANCER

Ms. Pelosi. A major concern of many women and their families is how best to respond when faced with a diagnosis of breast cancer. Frequently the woman and her family must make a choice about surgical or other treatment options that can prolong the length and quality of their lives. Is nursing research looking at how best to assist individual and families facing this situation?

Dr. Hinshaw: NINR is supporting several studies to determine how nurses can best assist women to work through their breast cancer experience. For example, one investigator has studied women undergoing breast biopsies and their husbands, following the couples for one year post surgery, in order to identify factors which put these couples at risk of severe distress and disrupted work, family and social functioning. This information will help nurses identify those women and their partners most at risk of difficulties coping with the breast cancer diagnosis and develop interventions to maximize their ability to deal with their experience.

Patient teaching is a major component of nursing care and an important opportunity for nurses to assist patients to assimilate and work through their illness experience. NINR has supported investigations of educational interventions designed to bolster patients' ability to cope with cancer and make informed decisions regarding their treatment. One current study is directed towards determining the extent to which an informational intervention guided by research and theory on coping can reduce negative emotional experiences and increase a patient's ability to use problem solving processes and coping strategies. Another investigator has examined the advantage of also providing educational interventions for family members and intimate friends of the patient undergoing treatment. Previous research has shown that patients retain only part of the information shared with them by health care providers. Informing family members can serve to reinforce information provided to the patient and increase the patient's ability to make sound decisions and cope with treatment complexities.

Another important area related to women's response to breast cancer is learning how to reach and appropriately assist vulnerable populations, such as the elderly, minority groups and those living in poor rural areas. For example, one NINR-supported group of investigators has developed the role of an oncology nurse case manager to provide older breast cancer patients with education, counseling, and help in arranging support services such as transportation, etc. The usefulness of this model of nursing care is being tested in eight South Texas hospitals to determine if these older women who receive the nursing case management intervention are more prepared and supported to obtain what is considered "usually appropriate" medical therapy rather than settling for suboptimal care.

SYMPTOM MANAGEMENT of HIV DISEASE

Ms. Pelosi. What kind of nursing research is currently being funded and what is planned with regard to symptom management with individuals with HIV disease.

Dr. Hinshaw: NINR's intramural program has established a foundation for interventions to alleviate symptoms and improve quality of life for AIDS patients. Intramural scientists are conducting several symptom management studies: one to describe the nature, extent and impact of nutrition-related changes during HIV treatment; another to examine the nature and impact of antiretroviral-associated muscle weakness; and a third to study the frequency, severity, duration and impact of fatigue in HIV-infected persons.

During FY 1994, this research will be expanded through an extramural initiative. A request for applications has been issued for preliminary investigations that will, in turn, lead to large-scale clinical studies of nursing interventions to improve the physical care of HIV-infected individuals. Issues to be addressed by these studies include: development of nonpharmacologic or multimodal management strategies to alleviate physical symptoms associated with HIV infection, complications and treatment; identification and mediation of underlying factors that explain differential responses to clinical conditions and treatment regimens; observations of the natural history or clinical course of physical symptoms during the progression of HIV infection and its treatment to identify variables that can be clinically manipulated to reduce the severity of symptoms; and development or refinement of instruments to assess physical symptoms and to monitor changes resulting from interventions to alleviate symptoms.

SYMPTOM MANAGEMENT

Ms. Lowey: I am particularly interested in your comments regarding the use of "in-tandem" therapy for cancer patients and others whose treatment involves painful and difficult procedures. Can you tell us more about the findings in this area and the clinical applications you foresee for this kind of therapy?

Dr. Hinshaw: Nurse scientists often seek to determine the effectiveness of nonpharmacological interventions to supplement pharmacological approaches to ease painful or difficult procedures and situations. The use of behavioral interventions to supplement antiemetics in the control of chemotherapy-related nausea and vomiting is an excellent example. Despite improvements in antiemetic treatments, over 70 percent of patients continue to experience nausea and vomiting during chemotherapy. NINR-supported investigators have learned that a behavioral intervention which teaches patients relaxation techniques to reduce the tension associated with chemotherapy treatments effectively reduces the nausea experienced by these individuals. This intervention has been particularly useful in reducing the experience of "anticipatory" nausea or nausea experienced during chemotherapy before the actual administration of cytotoxic drugs. Current work by this research team is aimed at predicting which chemotherapy patients are most like to develop anticipatory nausea so that behavioral interventions can be appropriately targeted.

The NINR has a special initiative on the assessment and management of acute pain. In addition to important considerations in the proper administration of pain medications, nurses can implement either physical measures or cognitive-behavioral measures to deal with pain. Physical agents such as heat, cold, massage, and transcutaneous electrical nerve stimulation have been the focus of research with some promising results, although additional work is needed to identify groups of patients who are most likely to benefit. Cognitive-behavioral measures include measures such as biofeedback, relaxation training, and educational interventions using procedural, sensory, and/or coping behaviors; more study is needed particularly for selected clinical conditions and population groups.

NINR is funding an ongoing study which is testing the effect of two nursing protocols on the intensity of postoperative pain in children, ages 3 to 7, of African-American, Hispanic, and European-American backgrounds. The researchers are testing interventions based on activation of central pain control mechanisms (i.e., distraction, diversion, relaxation techniques) and peripheral pain control mechanisms (i.e., touching, positioning, warm and cold applications) and comparing these interventions to standard nursing practices (talking soothingly, providing explanations, and giving medications).

WOMEN'S HEALTH INITIATIVE

Ms. Lowey: Is your Institute involved in the Women's Health Initiative?

Dr. Hinshaw: NINR staff were active participants in the development of the Women's Health Initiative and continue to participate on the Women's Health Coordinating Committee. Issues in women's health and reproductive health have historically been major foci of nursing research and of NINR research investments. NINR is currently planning an initiative on managing clinical symptoms common to women during midlife. We are also planning an initiative in FY 1995 on decision-making by women about treatments for noncancerous problems of the uterus. These problems frequently lead to women undergoing a hysterectomy, which is a frequently occurring and costly procedure about which we know little concerning the decision-making process and the surrounding processes of clinical care.

HEALTH CARE REFORM STUDIES

Ms. Lowey: You mentioned two studies that compared the outcomes of similar groups of patients treated by doctors and by nurses. Can you tell us more about these studies? What factors do you think contributed to the better outcomes for patients receiving nurse care? What are the implications of these findings for health care reform?

Dr. Hinshaw: One of these studies is comparing the efficacy of a special care unit for adults who have experienced a critical illness, such as pneumonia with respiratory failure, and have recovered from the most acute, unstable phase, but who still need intensive care, including continual mechanical ventilation. The study is also determining whether these patients need to be in regular intensive care units (ICUs) which are physician and nurse managed or whether special care units (SCUs) designated for their more chronically critically ill needs which is nurse managed with physician consultation as needed, and whether the SCU can provide comparable care at lower costs with improved health status. Preliminary findings from this study indicate that the clinical indicators are comparable for both sets of patients, that SCU patients have improved outcomes, and that costs to the hospital were less for SCU patients. This study will be completed later this year, and the final results will be available.

The other study is a comparison of the prenatal, delivery and post partum processes of care of Certified Nurse Midwives (CNM) and Obstetrical Physicians (OP). Preliminary findings indicate that these two clinical providers differ in their practices. CNMs thought it more important to screen for nutritional intake during pregnancy and more important to walk patients during labor than physicians. CNMs also considered it less important to do routine ultrasound; to use drugs to stimulate labor, intravenous fluids, continuous fetal monitoring during labor; and less important to deliver in the delivery room. As this study is still underway there are no clinical outcomes yet, however preliminary finding for charges indicate that the CNMs were lower.

Health care reform calls for prevention strategies and an increase in community-based care. As a financing mechanism to increase health care coverage, reform may lead to decisions about alternatives to traditional medical care that are shown to be of high quality, safe and comparable on clinical outcomes. Studies such as the ones described here need to continue to demonstrate ways to achieve alternatives to traditional high cost care. Nurse in advanced practice are positioned to provide such clinical care and to participate in clinical research.

HISPANIC EMPLOYMENT AND PROMOTION

Mr. Serrano. Dr. Hinshaw, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. First, I would appreciate you telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Hinshaw: Although the NINR is the smallest Institute at the NIH with only 52 FTEs, we are very proud of the recent accomplishments we have made in recruiting and hiring Hispanic employees. Currently, 4 percent of the NINR staff is Hispanic. We have recently hired a Hispanic male to serve as a GM-15 Chief of the NINR Office of Review. In terms of the steps we are taking to increase Hispanic hiring and promotion within NINR, we work closely with the NIH Office of Equal Opportunity and the Hispanic American Advisory Committee to help us identify qualified Hispanic candidates who may be interested in applying for our positions. In addition, we have established contact with the National Hispanic Nurses Association for assistance in recruiting Hispanics for positions within the NINR. We had also had regular consultations with the Hispanic Nurses Association meetings to inform the participants about the mission of the NINR, to establish contacts within the Hispanic community, and to try to interest some of the Hispanic nurse scientists in attendance to apply to us for research grant funding or to consider employment opportunities within the NINR.

HISPANIC HEALTH ISSUES

Mr. Serrano. Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Hinshaw: In FY 1993, 5.1 percent of NINR's total budget was directed specifically at Hispanic health issues. For example, health promotion and disease prevention is one of the major research emphases of NINR. One of the exploratory centers is focused on health promotion/disease prevention for Hispanic adolescents. The center is addressing questions on enhancing nutritional status and encouraging exercise for adolescents, on nursing interventions for pregnant adolescents to improve school progression and measures of health status of the newborn, and on improving oral health practices. The issues of compliance and adherence and how to determine the level of understanding of written materials have proved extremely important.

Another study is looking at the problem of diabetes. Hispanics experience non-insulin dependent diabetes three to five times more frequently than non-Hispanic whites. It is well-known that patient education is effective in improving outcomes in patients with non-insulin dependent diabetes. Investigators are developing materials and procedures which will be culturally sensitive and relevant in order to maximize participation and compliance with the recommendations for management of the condition.

HISPANICS IN BIOMEDICAL RESEARCH

Mr. Serrano. Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Hinshaw: The staff of NINR have regular meetings with the National Hispanic Nurses Association to share information about scientific activities and status of research training opportunities. NINR staff have also participated in a seminar in Puerto Rico discussing research and training opportunities at NIH and providing technical assistance. In addition, NINR stimulated the development of and leads the National Nursing Research Roundtable, a group of all nursing organizations with interest in research, that meets annually to discuss common interests. A specific area that is regularly included is discussion about successful ways to develop scientists from minority populations. At this time, NINR has supported only college-level minority students; we have not had activities at the high school level or lower grades.

RECRUITING AND RETAINING HISPANICS IN CLINICAL TRIALS

Mr. Serrano. Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Hinshaw: As the newest Institute at NIH, NINR does not yet fund any standard clinical trials. A very sizeable portion of NINR's extramural research support is invested in clinical research, and some of these investigations will lead us to questions and hypotheses for testing in full-scaled clinical trials. NINR has been focussed from its beginning on the importance of questions about the health of Hispanics and other minority populations and about the inclusion of all appropriate sub-populations in research patient and subject groups.

The National Institutes of Health has recently published a set of Guidelines for the Inclusion of Women and Minorities in clinical trials. NINR is making a special effort to inform all NINR-funded investigators and applicants about the Guidelines and the need to include all relevant populations in clinical research efforts. We are committed to supporting research investigations with design and recruitment procedures that recognize the diversity of the U.S. population.

HISPANIC INVESTIGATORS

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Hinshaw: NINR has taken aggressive steps to assist minorities to become skilled, competitive investigators. However, information about the minority status of all NIH applicants and awardees is an optional self-reported item on the application. The data available reveal that for NINR in FY 1993 there were three applications reviewed from Hispanic investigators. Of these, one application was funded, resulting in a success rate of 33.3 percent. This compares to NINR's overall success rate in FY 1993 of 11.3 percent.

THURSDAY, APRIL 21, 1994.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

NATIONAL EYE INSTITUTE

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

WITNESSES

DUANE F. ALEXANDER, M.D., DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

CARL KUPFER, M.D., DIRECTOR, NATIONAL EYE INSTITUTE

PHILLIP GORDEN, M.D., DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

ENOCH GORDIS, M.D., DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

INTRODUCTION OF WITNESSES

Mr. SMITH. Today we have the Eye Institute, Diabetes and Digestive and Kidney Diseases, and Child Health, and also Alcohol Abuse and Alcoholism.

Dr. VARMUS. Mr. Chairman, should I introduce my colleagues?

Mr. SMITH. Yes.

Dr. VARMUS. On the right we have Dr. Duane Alexander, who is the Director of the National Institute of Child Health and Human Development who will present first, followed by Dr. Carl Kupfer, who is Director of the National Eye Institute, celebrating his 25th anniversary as you will soon hear.

On my left is Dr. Phillip Gorden from the National Institute of Diabetes and Digestive and Kidney Diseases, and on my far left, Dr. Enoch Gordis, who is the Director of the National Institute on Alcohol Abuse and Alcoholism.

Mr. SMITH. Okay. Go ahead.

OPENING STATEMENT

Dr. ALEXANDER. Thank you, Mr. Chairman. The research of the National Institute of Child Health and Human Development addresses maternal and child health, reproduction, and medical rehabilitation. Among the exciting advances coming out of the Institute this year is the demonstration that a new drug, tin mesoporphyrin, SnMP, effectively prevents the development of jaundice in infants. Jaundice is common, expensive to treat and can cause mental retardation if not controlled. In another advance, our intramural scientists have pioneered a new innovative technique for performing surgery on babies while they are still in their mother's womb. The obstetricians who developed this life-saving technique are part of the Institute's Perinatal Research Branch, established recently in the District of Columbia as a result of a Congressional directive.

The Institute is about to embark on a major public education campaign to influence infant sleep position. Evidence indicates that infants who sleep on their back or side are far less likely to die of Sudden Infant Death Syndrome, or SIDS, the leading cause of infant death after one month of age. It is thought that a change in infant sleep position from stomach to back or side will result in a drop in the U.S. SIDS rate.

As mandated in the NIH Revitalization Act, the NICHD recently awarded a grant to support the first comprehensive national study of the determinants of adolescent health. The study will show what influences contribute to the development of the behaviors that affect health, such as alcohol use, eating habits, and sexual behavior.

The NICHD is taking advantage of remarkable advances in bioengineering and applying them to improving orthotic and prosthetic devices for persons with disabilities. Projects include the design of an electronic implant to convey sensation in artificial limbs, and efforts to improve prostheses currently used to correct the gait of children with cerebral palsy.

The NICHD, as part of its AIDS research program, has been working for several years to develop and test female controlled barrier contraceptives, as well as spermicides that are also microbicidal. Such products would protect against both pregnancy and sexually transmitted diseases, including HIV infection. The fiscal year 1995 budget request includes funds to expand this initiative.

With a portion of the additional AIDS funds requested, the NICHD will expand a national research effort on adolescent AIDS. One-quarter of all reported AIDS cases involve young adults 20 to 29 years of age and there are data that indicate that most of these individuals are infected with HIV while they are teenagers.

In another collaborative AIDS effort, NICHD helped design and fund the large clinical trial in which AZT therapy reduced by two-thirds the risk of transmission of the virus from HIV-infected women to their babies. We are now testing whether the addition of hyperimmune anti–HIV globulin to AZT in pregnancy can further reduce the transmission of HIV to the fetus, with the hope of eventually eliminating pediatric AIDS.

These are just a sampling of the many NICHD research highlights for this past year and plans for fiscal year 1995. All contribute to the betterment of our Nation's health, particularly that of its mothers and children, and have the added benefit of saving health care dollars as well. Mr. Chairman, our request, excluding AIDS, is $516.736 million for fiscal year 1995. I will be glad to answer any questions.

Mr. SMITH. Okay. Thank you, Dr. Alexander.

[The prepared statement and biography of Dr. Duane Alexander follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Child Health and Human Development

The mission of the National Institute of Child Health and Human Development (NICHD) is to assure that every individual is born healthy, is born wanted, and has the opportunity to fulfill his or her potential for a productive life unhampered by disease or disability. To fulfill this goal, the NICHD conducts and supports laboratory and clinical research on the reproductive, developmental, and behavioral processes that determine and maintain the health and well-being of children, adults, families, and populations. In addition, research in medical rehabilitation is supported to maximize the function of individuals with physical disabilities resulting from diseases, disorders, injuries or birth defects.

Some of the most exciting advances from the NICHD research program this year benefit our very youngest patients: newborn babies. For example, NICHD-supported scientists developed and tested a new drug that effectively prevents the development of jaundice in infants. The drug, called tin mesoporphyrin (SnMP), blocks the production of bilirubin, the yellow pigment that leads to severe jaundice when it builds up in the blood faster than the liver can process it. This drug is a simple, safe, rapid and inexpensive therapy to curb neonatal jaundice, the most commonly treated medical condition in preterm and fullterm newborns. This jaundice (hyperbilirubinemia) can lead to deafness and mental retardation if not rapidly controlled. The usual treatment is several days of intensive exposure to special lights, known as phototherapy. This involves an extended hospital stay. With this new therapy, a single, small dose of SnMP shortly after birth eliminates the need for phototherapy in most infants. In the U.S., about 250,000 infants each year develop jaundice severe enough to warrant phototherapy treatment. This new drug thus can alleviate a cause of both medical and parental concern and save health care dollars as well.

NICHD intramural scientists have pioneered an innovative technique for performing surgery on babies still in their mother's womb. This new procedure uses long, thin tubes, about the size of a pencil lead in diameter, inserted through the mother's abdomen to perform delicate surgery on malformed or otherwise at-risk fetuses. Previously, surgery on the unborn required a large incision in the mother's uterus and posed great risk for both mother and child. Very few of these earlier attempts were successful. This new technique minimizes the risk. As the investigators gain more experience and train others to utilize this procedure, their technique will greatly increase our access to the fetus for diagnosis and treatment.

The obstetricians who developed this technique are part of the Institute's new Perinatal Research Branch, established recently as a result of a Congressional directive and located in the District of Columbia. Research achievements such as this advance should greatly contribute to our understanding of fetal development and the management of high risk pregnancies. This understanding is essential to solving the persistent nationwide problem of infant mortality.

The NICHD, in conjunction with other Federal agencies and private sector organizations, is about to embark on a major public education campaign to influence infant sleep position. Evidence indicates that infants who sleep on their back or side are at reduced risk for Sudden Infant Death Syndrome (SIDS), the leading cause of infant death after one month of age. It is thought that if a change in infant sleep position from abdomen to back or side can be wrought in the U.S., the SIDS rate will drop as a result.

Birth defects are another leading cause of infant mortality. A long search for the genes that determine the pattern of early embryonic development succeeded this year. NICHD-supported scientists discovered several of the genes that direct the process of initial formation of the nervous system and limbs in mice and fruit flies. Identifying these genes, termed "hedgehog genes", represents a major advance in developmental biology. Study of their action, both normal and abnormal, should provide significant clues to the origin of birth defects in humans.

As mandated in the NIH Revitalization Act, the NICHD recently awarded a grant to support the first comprehensive national study of the determinants of adolescent health. The study will show what influences contribute to the development of behaviors that affect health, such as alcohol or tobacco use, seat belt or helmet use, exercise, or sexual behavior. Some 160 middle and high schools and 19,000 students and their parents will be involved.

Between 35 and 43 million Americans have one or more conditions that limit their life activities. The NICHD's National Center for Medical Rehabilitation Research is taking advantage of remarkable advances in bioengineering and applying them to enhancing the independence and quality of life of persons with physical disabilities. Projects include the development of computer software to aid in the proper fitting of artificial limbs, the design of an electronic implant to convey sensation in artificial limbs, and the development of a high quality, robotic arm for below-elbow amputees. Other NCMRR-sponsored projects in the prosthetics/orthotics field include efforts to improve the knee joints of prosthetic legs and the gripping mechanisms of prosthetic hands, and to improve the orthoses currently used to correct the gait of children with cerebral palsy.

Women's health is a major focus of NICHD research. Scientists we supported are making progress toward elucidating the biology of endometriosis, a poorly understood condition that affects about 10 percent of U.S. women of reproductive age. These investigators have found that a significant number of endometriosis patients have abnormalities of a class of proteins called integrins. Since integrins are a family of proteins involved in cell attachment and invasion, they may prove to have a role in the process by which uterine cells implant and grow in inappropriate sites as endometriosis lesions, as well as in the infertility associated with the disease.

The NICHD, as part of its AIDS research program, has been working for several years to develop and test female controlled barrier contraceptives, as well as spermicides that would also be microbicidal. Such products would protect against both pregnancy and sexually transmitted diseases, including HIV infection. The FY 1995 budget request includes funds to expand this initiative, which is being conducted in concert with the National Institute of Allergy and Infectious Diseases. It will allow us to expand basic research on vaginal physiology and immunology and develop new, improved products and test them as quickly as possible through NICHD's soon to-be-established Contraceptive Testing Network. We will also study the behavioral factors that affect the acceptability and effective use of female-controlled barrier contraceptives and spermicides.

With a portion of the additional AIDS funds requested, NICHD will expand a national research effort on adolescent AIDS. One quarter of all reported AIDS cases involve young adults 20 to 29 years of age, and there are data to indicate that an increasing number of individuals are being infected with HIV as teens.

In another collaborative AIDS effort, NICHD helped design and fund the large clinical trial in which zidovudine (AZT) therapy reduced by two-thirds the risk of transmission of virus from HIV-infected women to their babies. The results of this trial were so compelling that the trial was terminated early so that AZT can be offered to all pregnant women as soon as possible. Although this treatment did not protect all the babies in the study, the results are very promising. We are now testing whether the addition of hyperimmune anti-HIV globulin to AZT treatment in pregnancy can further reduce HIV transmission to the fetus, with the hope of ending pediatric AIDS.

These are just a sampling of the many NICHD research highlights for this past year and plans for FY 1995. All contribute to the betterment of our nation's health, particularly that of its mothers and children, and have the added benefit of saving health care dollars as well. Mr. Chairman, the NICHD requests $516,736,000 for FY 1995. I would be glad to answer any questions.

CURRICULUM VITAE

NAME	Duane Frederick Alexander, M.D.
BIRTH	August 11, 1940, Baltimore, Maryland
MARITAL STATUS	Married Marianne Ellis, Washington D.C., June 23, 1963; two children
EDUCATION	Pennsylvania State University, University Park, Pennsylvania, B.S. Degree, Pre-Medical, 1962 Johns Hopkins University School of Medicine, Baltimore, Maryland, M.D. Degree, 1966
INTERNSHIP	Intern and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1966-1967
RESIDENCY	Assistant Resident and Fellow, Department of Pediatrics, Harriet Lane Service, Johns Hopkins Hospital, 1967-1968
MILITARY SERVICE	1968-1970: Surgeon (LCDR), U.S. Public Health Service, and Clinical Associate, Children's Diagnostic and Study Branch, National Institute of Child Health and Human Development, (NICHD) National Institutes of Health (NIH) Bethesda, Maryland 1971-Present: From Surgeon to Assistant Surgeon General, U.S. Public Health Service
FELLOWSHIP	Fellow in Pediatrics (Developmental Disabilities), John F. Kennedy Institute for Habilitation of the Mentally and Physically Handicapped Child, Johns Hopkins Hospital, 1970-71
LICENSURE	Maryland Board of Medical Examiners
CERTIFICATION	Diplomate, American Board of Pediatrics, 1973
POSITIONS HELD	
1971-74	Assistant to the Scientific Director, NICHD, NIH, Bethesda, Maryland
1974-78	Medical Officer (Staff), National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, DHEW
1978-82	Assistant to the Director, NICHD, NIH
1982-86	Deputy Director, NICHD, NIH
1986-present	Director, NICHD, NIH

OPENING STATEMENT

Dr. KUPFER. Mr. Chairman, I would like to submit my written statement for the record and just make a brief presentation. The role of the National Eye Institute is to preserve vision amongst Americans of all ages, and the challenges implicit in this goal.

First of all, there are more than 130 million Americans who wear glasses, 10 million who have serious visual disability, 1 million who are legally blind, and the cost to society of visual disability and blindness is approximately $38 billion a year.

One of the challenges that we face is that our population is aging. At the present time, there are 32 million Americans over the age of 65 and by the year 2030, this figure will more than double to nearly 66 million Americans.

We are on the verge of an epidemic in dealing with a number of age-related eye diseases, one of which is age-related macular degeneration. At the present time, there are almost 2 million Americans who have lost central vision from macular degeneration. What is lost with central vision is the ability to drive an automobile, read the newspaper, or even watch television.

By the year 2030, the number with macular degeneration will increase to more than 6 million Americans. So we are really confronting the issue of the aging population. We have completed one clinical trial which shows that we can prevent the loss of vision in the 10 percent of patients having neovascular or "wet" form of age-related macular degeneration, but that leaves us with 90 percent who have the dry form for which we have no treatment approach.

We are approaching this problem on two fronts. One is through basic research in the laboratory where we are looking at transplantation of cells from the retina, gene therapy, microsurgery, and drug therapy. The other is at the clinical level, where we are conducting a clinical trial to see whether vitamin supplements and/or minerals can be of benefit in slowing down the loss of vision.

We would like to see this clinical trial result in proven treatments similar to what has been done with another age-related eye disease, diabetic retinopathy where we have been able to reduce the rates of blindness from 50 percent to less than 5 percent.

The other two age-related diseases that we are grappling with are cataracts and glaucoma. To continue all of our activities to preserve vision, the National Eye Institute is requesting for fiscal year 1995, $292 million excluding AIDS funding. I would be happy to answer any questions.

[The prepared statement and biography of Dr. Carl Kupfer follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Eye Institute

Mr. Chairman, I am pleased to report that the NEI is now in the first year of its sixth long-range plan. As I have mentioned in previous years, the NEI places a premium on strategic planning to identify future needs and opportunities in vision research. I would like to share with the Committee some of the initiatives that are now underway as a result of this national planning activity and some recent findings that our previous planning efforts have helped to facilitate.

Historically, the NEI has sought to invest its resources in areas that appear ready to yield rapid advances. This was the rationale for our investigations in the 1970s on the use of laser surgery as a treatment for diabetic retinopathy. It was reported this year that this treatment now saves the Federal government between $1.2 and $1.6 billion annually.

Through our recent planning process, the NEI has identified glaucoma research as one of several areas of great opportunity. Glaucoma, which affects three million Americans and is particularly prevalent among African Americans, damages the optic nerve and is often associated with increased pressure at the front of the eye. During the past several years, glaucoma researchers have produced important new epidemiologic data, state-of-the-art diagnostic techniques, and improved medical and surgical treatments.

But this progress must be followed up. To seize this opportunity, the NEI recently launched three large clinical trials on glaucoma. These studies will produce objective, scientifically validated information on the disease's natural history, risk factors, diagnosis, and treatment. We anticipate that this investment will provide practitioners with improved strategies for patient care and could eventually save the Federal government millions of dollars in disability-related payments.

The NEI also recognizes that glaucoma's prevention, diagnosis, and treatment will only be enhanced with an improved understanding of the disease process. I am pleased to report that NEI-supported basic research on glaucoma yielded some promising leads last year. One group reported that a novel neurotransmitter lowers the pressure in the eye. This finding now opens the door to a possible new therapeutic approach to reduce pressure and prevent optic nerve damage. Other NEI-supported researchers determined the chromosomal location of a gene responsible for a form of juvenile glaucoma. This is the first glaucoma-causing gene ever mapped. Although the link between juvenile-onset glaucoma and the more prevalent primary open-angle glaucoma needs further elucidation, this development could lead to greater understanding of the disease process.

Another excellent research opportunity is the role of vitamin/mineral supplements in the treatment of cataract and age-related macular degeneration (AMD). By the year 2030, more than 66 million Americans will be at risk for these common eye diseases of aging. If an easily administered, daily vitamin/mineral supplement could protect people from these diseases before more rigorous and costly therapy is required, it would have enormous public health implications.

To investigate this possibility, the NEI has launched the Age-Related Eye Diseases Study (AREDS), a multi-center clinical study and trial involving 4,400 older Americans. The AREDS will provide patients and practitioners with the most definitive information yet regarding the safety and effectiveness of this possible treatment.

The NEI continues to investigate other promising strategies to prevent age-related eye diseases. In the early 1980s, there were fewer than 250,000 cataract operations performed each year in the United States. In less than 15 years, this number has jumped to more than 1.5 million cataract surgeries per year at a cost exceeding $5 billion. Reimbursement for cataract surgery now accounts for 12 percent of the Medicare Part B budget. I must add that by the year 2030, there will be a need for 2.3 million cataract surgeries per year, a demand that will be extremely difficult for any health care system to meet.

However, if cataract development could be delayed by just 10 years, the need for cataract surgery would decrease by almost half. One way to delay cataract is to develop drugs that act to slow down the disease process. The NEI is now supporting several studies on the study of drugs that counteract oxidative damage, which is thought to be an important factor in cataract development.

I am also pleased to report this year that NEI-supported scientists reported recently that most adults with retinitis pigmentosa (RP) should take a daily 15,000 IU vitamin A supplement. This recommendation is the first from a well-designed clinical trial demonstrating that the 100,000 Americans with this blinding retinal disease can be treated. However, the scientists also found that high-dose vitamin E supplements appeared to cause the disease to progress more quickly. Prior to publication of these findings, the NEI issued a "Dear Colleague" letter to approximately 36,000 eye care professionals nationwide that prepared them for future consultations with their RP patients. Retinitis pigmentosa research is now among the most productive areas of basic vision research. With the recent explosion in biotechnology, scientists can now isolate a defective, RP-causing gene by studying blood samples from families with a history of the disease. Such studies already have led to the discovery of more than 40 mutations in several retinal genes that are responsible for several forms of RP. The scientific opportunities to develop clinical strategies for early diagnosis, genetic counseling, and treatments, such as gene therapy, are now well within reach.

This year, the Diabetes Control and Complications Trial reported that people with diabetes who tightly controlled their blood glucose levels greatly decreased their chances of having the eye, nerve, and kidney complications of diabetes. Unfortunately, many people with diabetes will not escape the complications of the disease. Complementary approaches are now needed to help protect the health of people with diabetes.

For this reason, the NEI continues to develop drugs that inhibit the enzyme aldose reductase, which has been linked to the eye and nerve complications of diabetes. NEI intramural researchers are developing new aldose reductase inhibitors using biochemical, pharmacological, and computer design techniques. These new drugs are needed to eliminate the side effects and improve upon the first generation of aldose reductase-inhibiting drugs. Recently, the NEI and the Juvenile Diabetes Foundation International initiated a $4 million cooperative program to stimulate basic research on the cellular and molecular basis of diabetic retinopathy.

The NEI is also making important strides in understanding disorders involving the processes by which visual signals are sent to the brain. In the visual system, there is a precise pattern of connections between the retina at the back of the eye and the brain. This pattern is established and refined during early life. Scientists have shown recently that certain chemical signals are needed at the right time and place for infants to develop normal vision. Determining the nature of these signals may lead to new treatments to repair developmental abnormalities, such as crossed eye and lazy eye. As many as 5 percent of Americans now have crossed eye, lazy eye, or abnormal visual processing.

Research on myopia, or nearsightedness, which affects 25 percent of Americans, has moved ahead very rapidly in the laboratory. Scientists have learned a great deal about what seems to control the size and shape of the eye, since an eye that is too large causes most myopia. How generalizable this information will be to humans is still unclear. But, for the first time, researchers are designing experiments to test these theories and to determine whether nearsightedness is preventable.

I am pleased to report the NEI-coordinated National Eye Health Education Program is making excellent progress in expanding its activities to alert Hispanics about diabetic eye disease, a leading causes of preventable blindness in this group. The NEHEP has also recently supported a two-year pilot program to increase eye health education among African Americans in Durham, North Carolina and Cleveland, Ohio.

The NEI also continues to study the possible causes of dry eye, which affects millions of middle-aged and older women. The institute sponsored a workshop last year and is actively encouraging the submission of research grant applications to investigate this condition.

Mr. Chairman, the FY 1995 budget request for the National Eye Institute is $292,022,000. I will gladly answer any questions that the Committee might have.

CARL KUPFER, M.D., Director, National Eye Institute
February 9, 1928. New York, New York.

Education: A.B., Yale Univ., 1945-48. M.D., The Johns Hopkins Medical School, 1952 Certified. American Board of Ophthalmology, 1958.

Professional History: Internship and Assistant Residency, Wilmer Eye Inst., Johns Hopkins (JH) Hospital, 1952-54. Lab. Asst., Biostat., JH School of Medicine, 1953-58. Research Fellow in Ophth., Harvard Medical School, 1958-60. Instructor in Ophthalmology, Harvard Medical School, 1960-62. Assistant Professor of Ophthalmology, Harvard Medical School, 1962-66. Prof. and Chairman in Ophth., Univ. of Washington School of Medicine; Research Affiliate, Univ. of Washington Primate Ctr., 1966-70. Director, National Eye Institute, 1970-present. Acting Deputy Director for Intramural Research, NIH, 1991-1992.

Professional Organizations: Am. Physiological Society; Assoc. for Research in Vision and Ophth.; Am. Academy of Ophthalmology; Am. Ophthalmological Society; Pan Am. Ophth. Society; Johns Hopkins Univ. Soc. of Scholars; Member, Inst. of Medicine, National Academy of Sciences.

Honors and Awards: The Secretary's Special Citation, DHEW, 1972; The Superior Service Award, DHEW, 1974; Presidential Rank Award of Meritorious Executives, 1983; Migel Medal, Amer. Foundation for the Blind, 1976; Public Service Award in Ophth., Amer. Academy of Ophth. and Otolaryngology, 1977; Special Award of Honor, The Assn. for Research in Vision and Ophthalmology (ARVO), 1983; David Rumbough Memorial Scientific Award, JDF, 1983; The Lighthouse Pisart Vision Award, 1984; Cavera Medal of Univ. of Rome, 1985; The Mildred Weisenfeld Award for Excellence in Ophth. 1987; Presidential Distinguised Rank Award, 1991; Statesmenship Award, Joint Commission on Allied Health Personnel in Ophthalmology, 1991; Lions Clubs Intl. Humanitarian Award, 1992; Kupfer Award of the ARVO, 1993; Leadership Award, AOS, 1993; Benjamin F. Boyd Humanitarian Award of the Pan-Am. Assn. of Ophthalmology, 1993; Joslin Diabetes Center-MediSense Award, 1994.

Other Scientific Activities: Editorial Board, Investigative Ophth., 1969-1977; Editorial Board, Am. Journal of Ophth., 1971-1983; Member, Scientific Advisory Committee, Fight for Sight, 1971-present; Member, National Diabetes Advisory Board, 1976-present.

International Appointments: Member, Board of Trustees, HKI, Inc., 1975-present; Member, Intl. Vitamin A Consultative Group, WHO, 1973-present; Member, WHO Advisory Group for Prevention of Blindness Prog., 1978-1984; Consultant, Pan Am. Health Organization, 1978-present; Coordinator for USA, Priority Area "Eye Diseases," U.S.-U.S.S.R. Prog. for Health Cooperation, 1978-present; Member, WHO Expert Advisory Panel on Trachoma and Prevention of Blindness, 1979-present; Dir., WHO Collaborating Ctr. for the Prevention of Blindness, National Eye Inst., Bethesda, MD, 1979-present; Pres., Intl. Agency for the Prevention of Blindness, October 1982-1990. Consultant in India for the World Bank, 1992-present.

OPENING STATEMENT

Dr. GORDEN. Mr. Chairman, I am pleased to highlight the research progress and plans of the NIDDK in combating many of the Nation's most serious, chronic, and costly diseases including diabetes, endocrine and metabolic diseases, digestive and nutritional disorders, kidney, blood, and urologic diseases. Achievements in these clinical areas rest on a solid foundation of basic research. Approximately 85 percent of our resources are expended in the extramural grant and training programs and approximately 11 percent of our resources in our intramural program. A strong, cross-cutting agenda in basic research underpins our clinical programs in prevention and treatment.

DIABETES CONTROL AND COMPLICATIONS TRIAL

Two recent advances have enormous implications for clinical management of diabetes. First, the multicenter NIDDK "Diabetes Control and Complication Trial" as mentioned by Dr. Varmus, concluded that complications of diabetes, such as blindness and kidney disease, can be prevented or delayed in insulin-dependent diabetes. A second prevention landmark is the discovery that bloodpressure lowering drugs like captopril have a beneficial effect on the kidney disease of insulin-dependent diabetes. We are prepared now to initiate an outreach program to educate health professionals and the public about the treatment of diabetes. In addition, we are launching new clinical trials attempting to prevent or delay the onset of insulin-dependent and noninsulin-dependent diabetes in susceptible individuals. Underpinning this is a basic research effort searching for the genes that cause both forms of diabetes.

Another example of this interactive approach is the successful use of gene therapy to treat muscular dystrophy in genetically predisposed mice. This is paralleled by the use of gene therapy techniques to treat genetically-induced high cholesterol disorders and other diseases such as cystic fibrosis.

DUODENAL ULCERS

Prevention is the highlight of our digestive diseases research program. A recent NIH Consensus Development Conference concluded that the use of antibiotics to eradicate ulcer-causing bacteria essentially cures the disease and prevents its recurrence in most individuals. This should result in substantial cost savings. We have also found a new family of peptides that may play an important role in stimulating healing of the intestinal wall in inflammatory bowel disease. The Institute is enhancing trans-NIH nutrition research through leadership of the Division of Nutrition Research and Coordination and through the development of NIH-wide initiatives. We are extending our major initiative on prevention and treatment of obesity, including an important new clinical trial on "Long-Term Outcome of Obesity Treatment in Minority Women." This will be cosponsored with the NIH Office of Research on Minority Health.

KIDNEY UROLOGIC AND BLOOD DISEASES

Another goal is prevention of end-stage renal disease. A full scale clinical trial will study therapies for hypertensive kidney disease in

African-Americans. Fundamental studies are aimed at understanding and preventing the progression of different types of kidney diseases, such as polycystic kidney disease, IgA nephropathy and others to renal failure. To combat urologic diseases, a pilot clinical trial will examine the effectiveness of alternative drug and surgical treatments for abnormal enlargement of the prostate. Three new George O'Brien Kidney and Urologic Research Centers address prostate disease, a focus of productive NIDDK collaboration with the National Cancer Institute. In women's urologic disorders, the NIDDK is recruiting more than 1,300 people for the National Interstitial Cystitis Database Study. To promote multidisciplinary advances, we will establish up to three new molecular hematology research centers.

Mr. Chairman, the budget request for NIDDK for fiscal year 1995 is $742.547 million. I would be pleased to answer any questions.

[The prepared statement and biography of Dr. Phillip Gorden follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Statement of the Director
National Institute of Diabetes and Digestive and Kidney Diseases

I am pleased to highlight the research progress and plans of the NIDDK in combating many of the Nation's most serious, chronic and costly health problems, including: diabetes and metabolic diseases; digestive diseases; kidney and blood disorders; and urologic disorders. Uniting these clinical areas is a solid foundation of basic research on the nutrition sciences, endocrinology, molecular genetics, immunology, virology and other fields.

The NIDDK is strongly committed to research on both insulin-dependent and non-insulin dependent diabetes, which affect an estimated 14 million Americans at an annual cost of over $90 billion. Both forms of the disease are insidious, with long-term complications that include blindness, nerve damage, limb amputations, kidney failure and heart disease.

Two of our most recent research advances have enormous implications for improved clinical management of diabetic complications. First, the multicenter NIDDK "Diabetes Control and Complications Trial," concluded that complications damaging the small blood vessels can be prevented or delayed in insulin-dependent diabetes. The key is to maintain blood glucose levels as close to normal as possible. In this ten-year study involving over 1,400 people, intensive therapy reduced by 76 percent the risk for developing diabetic eye disease, and greatly delayed the onset and slowed the progression of kidney and nerve damage. A second prevention landmark is the discovery that the blood-pressure lowering drug captopril has a beneficial effect on the kidney disease of insulin-dependent diabetes. Results of this clinical trial were dramatic: a 50 percent reduction in the combined risk of death, dialysis or transplantation. In February, FDA approved captopril for diabetic kidney disease. This treatment could save an estimated $2.6 billion in dialysis costs over 10 years.

In parallel with the fight against diabetic complications, we are continuing vigorous research to understand and prevent the onset of diabetes itself. In highly promising basic studies, scientists have found that injection of an enzyme called GAD prevented the development of insulin-dependent diabetes in mice prone to this disease. This research suggests that GAD may have therapeutic potential in susceptible children and young adults. Basic research in experimental animals forms the basis of a new clinical trial to assess whether prophylactic use of low-dose intravenous or oral insulin can prevent or delay the onset of insulin-dependent diabetes in individuals who have both biologic markers and family histories predictive of the disease. In non-insulin-dependent diabetes, which disproportionately affects our minority populations, an exciting new NIDDK initiative is a full-scale randomized clinical trial aimed at preventing or delaying disease onset. This study derives from basic studies in experimental animals and patients that have delineated a focus for this preventive strategy. A cornerstone of our efforts to prevent the onset of both forms of diabetes is the search for disease-causing genes. We are making progress in identifying candidate genes and in harnessing broad scientific expertise through our Diabetes Interdisciplinary Research Programs and Research Centers Programs.

Prevention is also a theme of our research on digestive diseases, including ulcers, inflammatory bowel disease and liver disease. A recent NIH Consensus Development Conference concluded that the use of antibiotics to eradicate ulcer-causing bacteria essentially cures the disease and prevents its recurrence in most individuals. Because long-term bacterial infection has been linked to gastric cancer, additional research is needed to determine if the new treatment also may aid cancer prevention. Use of this inexpensive drug therapy could save billions of dollars annually in health care costs. In basic digestive diseases research with a prevention focus, NIDDK-funded scientists have discovered that inflammatory bowel disease (IBD) may be related to a newly discovered family of gastrointestinal "trefoil" peptides, which may have a role in stimulating healing. This advance typifies the kind of molecular understanding of disease that is needed to treat and prevent IBD. In liver research, we are beginning to understand how cells from transplanted livers may migrate into other tissues of the body, providing extra therapeutic benefits and potentially increasing immune tolerance of the transplanted organ. This research may shed light on ways to prevent transplant rejection. We are encouraged by these and other examples of recent progress in digestive diseases research. At the same time, however, this past year has witnessed an enormous tragedy at the NIH -- the deaths of five patients who participated in a clinical trial of the drug FIAU. This drug had appeared to be a promising treatment of these patients with liver disease due to chronic hepatitis B infection. The tragedy caused by the unexpected and unrelenting toxicity of FIAU has touched us all very deeply and underscored the complexities of clinical research.

In kidney disease research, a continuing goal is prevention of end-stage renal disease (ESRD), whose treatment costs exceed $10 billion annually under the Federal Medicare Program for dialysis and transplantation. Following a successful pilot study, we are about to begin the full scale clinical trial of therapies for one of the most common causes of kidney failure in African-Americans: hypertensive kidney disease. In addition, we are launching a full scale trial aimed at preventing excess morbidity and mortality in hemodialysis patients. At the core of our kidney diseases research program are fundamental studies aimed at preventing the progression of different types of kidney disease--such as polycystic kidney disease and IgA nephropathy--to irreversible kidney failure. For example, we recently completed a multicenter prevention-oriented clinical trial, the study of "Modification of Diet in Renal Disease (MDRD)." This study concluded that blood-pressure control has a beneficial effect on the progression of certain types of renal disease.

The nutrition sciences offer promise of preventing or mitigating many health problems. As the principal NIH institute for nutrition, the NIDDK is enhancing trans-NIH coordination of the field through leadership of the Division of Nutrition Research and Coordination and through the development of NIH-wide scientific initiatives. An example of important nutrition research is studies of zinc, which is believed to be important in the immune response.

The Institute is continuing to extend its major initiative on prevention and treatment of obesity, a serious health problem of increasing prevalence, and a risk factor for diseases such as insulin-dependent diabetes, heart disease and gallstones. The cost of obesity treatments alone is almost $40 billion per year, and treatment of associated disease complications costs billions more. The National Task Force on Prevention and Treatment of Obesity has prepared a draft report on "Obesity Research Directions" that includes a recommendation that NIDDK undertake a prevention initiative in obesity research. We have already begun this effort by co-sponsoring, with the NIH Office of Research on Minority Health, an important new clinical trial on "Longterm Outcome of Obesity Treatment in Minority Women."

Gene therapy is one of the most exciting approaches to treating serious genetic disorders. Recently, NIDDK-funded researchers made a substantial gain toward gene therapy for muscular dystrophy. Embryos of mice with a damaged dystrophin gene, which would have led to a form of muscular dystrophy, were altered by insertion of a reduced-size version of the correct gene. These embryos developed into healthy mice with undamaged muscles. Although the challenge of administering this therapy to human cells is great, this success demonstrates the possibility of correcting the genetic defect.

While investigators continue to work toward gene therapy for cystic fibrosis (CF), patients will be helped by the development of an exciting range of new therapies. Particularly important advances include the development of the drug DNase to help digest the sticky mucus that clogs the lungs, the aerosol delivery of the antibiotic tobramycin, and a new device to vibrate airway walls and loosen mucus.

Combating urologic diseases is a central goal of NIDDK. Abnormal enlargement of the prostate gland affects most men over the age of 50 and may be related to the development of prostate cancer in some cases. NIDDK has launched the pilot phase of a clinical trial to examine the effectiveness of alternative drug and surgical treatments for this condition. Three new George O'Brien Kidney and Urologic Research Centers focus on prostate growth, including cancer, and we continue to work in a productive collaboration with the National Cancer Institute. Urologic researchers have characterized receptors for small peptides called endothelins, which are found in the bladder and other tissues. They are investigating the potential link of these substances to a range of urologic problems such as impotence and bladder irritability. Likewise, researchers have identified a protein similar to nerve growth factor that is produced in smooth muscle cells of the prostate, binds to a specific receptor on nearby epithelial cells and thus may be involved in proliferation of prostate cells. Exploiting these findings may lead to new treatments for various urologic disorders. In women's urologic disorders, the NIDDK is recruiting more than 1,300 people for the National Interstitial Cystitis Database Study.

NIDDK intramural scientists have been at the forefront of research on red blood cells over the past two decades, gaining vital knowledge about how genes are turned on and off. They have recently discovered the existence of "gene insulators," which are special genetic sequences at the boundary between active and inactive genes. Ultimately, these insulator sequences may lead to improved techniques of human gene therapy, by protecting genetic material inserted therapeutically into a patient's DNA from inappropriate regulation. This kind of basic research is a foundation for future clinical advances. Progress has also been made in refining techniques of bone marrow transplantation to combat the cancer which commonly recurs due to undetected surviving malignant cells. Now, a new assay using PCR technology can assess post-transplant residual cancer cells and predict relapse. To promote additional multidisciplinary advances in blood research, the NIDDK will establish up to three new molecular hematology centers in FY 1994.

Mr. Chairman, the budget request for NIDDK for FY 1995 is $742,547,000. I would be pleased to answer any questions you may have.

Phillip Gorden, M.D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases

December 22, 1934. Baldwyn, Mississippi. Married, two children.

Education: B.A., Vanderbilt University, Nashville, Tennessee, 1957;

M.D., Vanderbilt University School of Medicine, Nashville, Tennessee, 1961.

Professional History: 1961-62, Intern, Yale University, New Haven, Connecticut. 1962-64, Assistant Resident, Yale University, New Haven, Connecticut. 1964-65, USPHS Clinical Fellow in Metabolism, Yale University, New Haven, Connecticut. 1965-66, USPHS Research Fellow in Metabolism, Yale University, New Haven, Connecticut. 1966-74, Senior Investigator, Clinical Endocrinology Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. 1974-78, Senior Investigator, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1974-76, Clinical Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. 1976-78, Visiting Professor, Institute of Histology and Embryology, University of Geneva School of Medicine, Geneva, Switzerland. 1978-present, Chief, Section on Clinical and Cellular Biology, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1980-1986, Clinical Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1983-1989, Chief, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1986-present, Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Professional Organizations: American College of Physicians, American Diabetes Association, American Federation of Clinical Research, American Society for Clinical Investigation, Endocrine Society, American Society for Cell Biology, Association of American Physicians, American Society for Biochemistry and Molecular Biology.

Honors, Awards: Alpha Omega Alpha Medical Fraternity, 1961. Doctor of Medicine (Honoris Causa) - University of Geneva, Geneva, Switzerland, 1986. Public Health Service Distinguished Service Medal, 1986. Public Health Service Commendation Medal, 1988. Distinguished Alumnus Award and Medal, Vanderbilt Medical School, 1990. Istituto Rotariano per I'Italia Meridonale (IRIM) Award of the Rotary International, Naples, Italy, 1992. Public Information Award of the Juvenile Diabetes Foundation, International, 1992. National Scientific Leadership Award, Crohn's and Colitis Foundation of America, Inc., 1993. Public Health Service Surgeon General's Exemplary Service Medal, 1993.

OPENING STATEMENT

Dr. GORDIS. Mr. Chairman and Members of the subcommittee, I am pleased to be here with you today to discuss the research advances and fiscal year 1995 program directions of the Natonal Institute on Alcohol Abuse and Alcoholism, the Nation's preeminent Federal organization for biomedical and behavioral research to reduce alcohol morbidity and mortality.

Alcohol is a legal drug used by more Americans than any other drug, including tobacco, and is the Nation's number one drug of abuse. It accounts for more economic and social damage than all of the illegal drugs combined, costing the Nation $98 billion each year. More than any illegal drug, alcohol injures the human body pervasively. About 20 to 40 percent of all adult hospital beds in large urban hospitals are occupied by people being treated for the complications of drinking. However, through our research dissemination activities, the Nation is becoming increasingly aware of the dangers of excessive alcohol use for the individual, family, and society.

The core of the scientific enterprise is basic research. At NIAAA, the basic research studies comprise studies that include the body's major organ systems, as well as studies that run the spectrum of the human life cycle—from the fetus to the elderly. Studies in genetics, the nervous system, cellular and molecular biology, and immunology are conducted by our extramural and intramural scientists. NIAAA's unique role and contribution to the Nation's basic research effort is determining the pathological effect on cells, neurons, and genes of use, abuse, and addiction to alcohol. A prime example of the benefits of our basic research is the discovery in the 1970s of the fetal alcohol syndrome and the subsequent research which is elucidating the mechanisms of this syndrome and forming a basis for prevention and treatment activities.

NIAAA complements its basic research with behavioral and epidemiologic research and addresses the crucial questions on the causes, diagnosis, consequences, treatment and prevention of alcohol abuse and alcoholism. Much of the research in these domains forms a scientific basis for the formation of rational social policy.

NIAAA researchers have recently shown that genetics plays a major role in the transmission of alcoholism in women, just as it does in men. This advance will help us design new treatment and prevention strategies for women. Earlier research had been inconclusive.

In the area of medications development, we have good news to report. Two recent clinical trials have shown particularly promising results in treating alcoholics with naltrexone, an opioid antagonist. It was very effective in reducing both alcohol craving, alcohol consumption, and relapse. These results are very encouraging. Future advances in understanding brain chemistry and physiology will provide new pharmotherapeutic possibilities for treatment of the alcohol dependence. In fact I believe this ushers in a new era in which pharmacology will combine with the traditional verbal therapies. It also illustrates the continuing importance of clinical trials in bringing basic research to bedside and to treatment.

The development of medication for the treatment of cirrhosis and alcohol-induced hypertension is also on the horizon. NIAAA has shown that alcohol is the direct toxin in alcoholic liver disease and that a specific form of collagen protein is associated with the risk of cirrhosis—the nineth leading cause of death in the country. The possibility now exists that medications can be developed to reduce or even reverse the scarring of the liver.

In the area of prevention, alcohol-related traffic fatalities remain the number one cause of death for youth. I am happy to say that NIAAA's studies have reported that legislation that raised the minimum drinking age to 21, for which the Institute provided the scientific basis, dramatically reduced alcohol-related driving deaths, especially among persons 16 to 20 years of age.

TRENDS IN ALCOHOL RESEARCH

An increase during the past several years in new techniques and technology for brain imaging now enables an unprecedented look at how alcohol affects the brain, for example, the brain of children in utero. Studies have revealed fairly consistent alterations in the basal ganglia, a region that controls some of the behaviors affected by alcohol exposure. This insight may lead to more sensitive diagnostic tools to detect cognitive defects due to fetal alcohol exposure.

In fiscal year 1995 under the President's request, NIAAA is organizing its research efforts on areas that target special populations as well as the population as a whole. These areas are women's health, medications development, health services research, minority health, youth, and prevention. These are broad areas, extending from molecular biology to economics and social policy. A critical need for new knowledge and great potential for significant advances characterize this research. There is mounting evidence that women who abuse alcohol have greater risk than men of developing cardiovascular disease, hemorrhagic stroke, reproductive and endocrine anomalies, and breast cancer. The Institute will expand its current research on alcohol's role in these diseases as well as investigate the mechanism of increased vulnerability. As alluded to previously, research on medication development is also moving along on several spheres.

The impact of alcohol abuse and alcoholism on children and youth is profound. There are direct and lasting effects of Fetal Alcohol Syndrome (FAS) on afflicted children; and the possibility that alcohol dramatically affects the physiological, social, and interpersonal development of youth during adolescence. These are topics that need further research. We are investigating the cellular and molecular mechanisms contributing to FAS, and the effects of alcohol on normal hormonal activation during puberty, as well as the development of gender differences in behavior and physiology.

Congress has mandated that we set aside a portion of our budget for health services research. We are doing so. We are studying various impacts of financial organization, cost structure of treatment services, managed care, and a variety of other very important issues related to outcomes and cost savings.

Our expertise in the cost benefit analysis of alcohol treatment contributed in part to the inclusion of alcoholism treatment benefits in the President's submission for health care reform.

Finally, in the area of prevention research NIAAA researchers are working to determine the family, socio-cultural, legal, and other environmental triggers that can interact with individual vulnerability and result in alcohol abuse and alcoholism. We are especially interested in supporting research in these areas in minority communities which in some cases have disproportionate problems with alcohol. Areas of research that will be expanded are studies that will determine special treatment needs that may exist for these communities, and studies that explore the unique genetic, socio-cultural and environmental factors that increase or decrease the risk of alcoholism and related pathologies.

Mr. Chairman, the request for NIAAA is $182.498 million, excluding AIDS. We will be pleased to answer any questions you may have.

[The prepared statement and biography of Dr. Enoch Gordis follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Alcohol Abuse and Alcoholism

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here with you today to discuss the research advances and FY 1995 program directions of the National Institute on Alcohol Abuse and Alcoholism, the Nation's preeminent Federal organization for biomedical and behavioral research to reduce alcohol morbidity and mortality. Our most recent and exciting discoveries I will highlight shortly.

Alcohol is a legal drug used by more Americans than any other drug, including tobacco, and is the Nation's number one drug of abuse. It accounts for more economic and social damage than all illegal drugs costing the Nation $98.6 billion each year. More than any illegal drug, alcohol injures the human body pervasively. However, through our research and research dissemination activities, the nation is becoming increasingly aware of the dangers of excessive alcohol use on the individual, family, and society.

The core of the scientific enterprise is basic research. Science seeks to uncover elemental knowledge of the human body -- and the nature of disease -- to enhance our ability to treat and prevent disease. Specifically at NIAAA, our basic research program is comprised of studies that include the body's major organ systems, as well as studies that run the spectrum of the human life cycle --- from the fetus to the elderly. Studies in genetics, the nervous system, cellular and molecular biology, and immunology are conducted by our extramural and intramural scientists. NIAAA's unique role and contribution to the Nation's basic research effort is determining the pathological effect on cells, neurons, and genes by the abuse of and addiction to alcohol. A prime example of the fruits of our basic research is our discovery in the 1970s of Fetal Alcohol Syndrome (FAS).

NIAAA complements its basic research program with behavioral and epidemiologic research and addresses the crucial questions on the causes, diagnosis, consequences, treatment and prevention of alcohol abuse and alcoholism. The results of NIAAA research have directly contributed to improved health for the population; decreased costs to society; and achievement of national goals.

NIAAA researchers have now shown that genetics plays a major role in the familial transmission of alcoholism in women, just as it does in men. This advance will help us design new treatment and prevention strategies for women. Earlier research was inconclusive about the genetic influence on women.

In the area of medications development we have good news to report. Two recent clinical trials have shown particularly promising results in treating alcoholics with naltrexone, an opiode antagonist.

It was very effective in reducing alcohol craving, alcohol consumption, and relapse. These results are very encouraging. Future advances in understanding brain chemistry and physiology will provide even new pharmotherapeutic possibilities for the treatment of dependent individuals.

The development of medications for the treatment of cirrhosis and alcohol-induced hypertension is also on the horizon. NIAAA research has revealed that alcohol is the direct toxin in alcoholic liver disease and that a specific form of collagen is associated with the risk of cirrhosis--the ninth leading cause of death in the country. The possibility now exists that medications can be developed to reduce or even reverse fibrosis of the liver. With regard to hypertension, our intramural researchers have recently discovered that alcohol inhibits a cardiovascular reflex by increasing the activity of a neurotransmitter known as GABA. We are optimistic that this knowledge is the first step toward medications to counteract the effects of alcohol on blood pressure.

In the area of prevention, alcohol-related traffic fatalities remain the number one cause of death for youth, but I am happy to say that NIAAA studies have reported that legislation that raised the minimum drinking age to 21 -- of which NIAAA research provided the scientific basis -- dramatically reduced alcohol-related driving deaths, especially among persons 16 to 20 years of age.

An increase during the past several years in new techniques and technologies for brain imaging now enables unprecedented look at the nature and mechanisms of the brains of FAS children. Studies have revealed fairly consistent alterations in the basal ganglia, a region that controls some of the behaviors affected by alcohol exposure. This provides us with new insight into the mechanisms of the central nervous system, and may lead to more sensitive diagnostic tools to detect cognitive deficits due to fetal alcohol exposure.

In FY 1995 under the President's request, NIAAA is focusing its research efforts on areas that target special populations as well as the population as a whole. These areas are: women's health, medications development, health services research, minority health, youth, and prevention. These research areas have a critical need for new knowledge and great potential for significant advances. There is mounting evidence that women who abuse alcohol also have a greater risk than men of developing cardiovascular disease, hemorrhagic stroke, reproductive and endocrine anomalies, and breast cancer. The Institute will expand its current research on alcohol's role in these diseases as well as investigating the mechanisms of increased vulnerability. NIAAA will also continue to support the largest and most in-depth longitudinal study of women's drinking ever conducted in the United States. Data from this study will provide information on the dynamics of women's drinking.

As alluded to previously, research on medications development to treat craving, withdrawal, and relapse; and alcoholic liver and other alcohol-related diseases are extremely promising and will receive continued high priority.

The impact of alcohol abuse and alcoholism on children and youth is profound. There are direct and lasting effects of FAS on afflicted children; and the possibility that alcohol dramatically affects the physiological, social, and interpersonal development of youth during adolescence. These are topics that need further research. NIAAA is investigating the cellular and molecular mechanisms contributing to FAS; and the effects of alcohol on normal hormonal activation during puberty, as well as the development of gender differences in behavior and physiology.

Health Services Research, an emerging area within alcohol research, focuses on evaluating the effectiveness and efficiency of prevention and treatment approaches for alcohol problems as they are implemented in real world settings. In our efforts to fully develop this area, NIAAA has organized its health services research activities into four areas: financing and reimbursement of services; effectiveness of services and client/patient outcomes; service utilization and costs; and delivery system organization and management. Our expertise on these issues contributed in part to the administration's health care reform proposal.

Prevention research at NIAAA is attempting to determine the family, socio-cultural, legal, and other environmental triggers that can interact with individual vulnerability and result in alcohol abuse and alcoholism. Advances in study designs make increasingly precise evaluations of interventions possible. Research on the economic influences that affect decisions to drink; the relationship of alcohol and violence, alcohol-related injuries; and FAS prevention efforts are receiving our continued support.

NIAAA-supported researchers are exploring alcohol problems in minorities and are striving to discover the genetic and environmental factors that place them at risk or protect them from alcohol problems. Some minority groups such as African Americans and Native Americans exhibit a higher prevalence of alcohol-related problems than Whites despite similar or lower rates of consumption. Areas of research that will be expanded are studies that will determine special treatment needs that may exist for minority communities; and studies that explore unique genetic, socio-cultural and environmental factors that increase or decrease the risk of alcoholism and related pathologies.

In closing, alcohol abuse and alcoholism have constituted major problems for humanity throughout history. Only in recent times has there been a concerted effort by science to discover the causes and develop effective treatment approaches and prevention measures. With the continued, committed efforts of alcohol researchers and our Institute, I am very optimistic that our future expectations to reduce the suffering of millions of people, and the associated economic and social costs of this severe public health problem will be realized.

Mr. Chairman, the FY 1995 request for NIAAA is $182,498,000, excluding AIDS. I will be pleased to answer any questions that you may have.

Enoch Gordis, M.D.
Director
National Institute on Alcohol Abuse and Alcoholism

Enoch Gordis, M.D., became the Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in October 1986. Prior to this, he was Professor of Clinical Medicine at Mt. Sinai School of Medicine, New York City, and a staff member of the Elmhurst Hospital in Elmhurst, N.Y., where he directed the hospital's alcoholism program from 1971 until his appointment to NIAAA.

The NIAAA, a part of the U.S. Department of Health and Human Services' (HHS) National Institutes of Health (NIH), is the principal Federal agency for research on the causes, consequences, treatment, and prevention, of alcohol-related problems. Through an intramural scientific program, which includes a 14-bed clinical research facility on the National Institutes of Health (NIH) Bethesda, Maryland Campus, and through an extensive array of extramural research grants and contracts, NIAAA supports studies in a variety of biological and behavioral areas such as, neurosciences, pharmacology, epidemiology, genetics, molecular biology, and prevention and treatment. The Institute also supports research training and health professions development programs, and research on alcohol-related public policies that provide HHS and other Federal, State, and local government decisionmakers with state-of-the-art analyses of the relationships between public policies and alcohol-related problems. The current NIAAA budget is $185.6 million.

Dr. Gordis received his M.D. degree from Columbia University in 1954, and trained in internal medicine at the Mount Sinai Hospital in New York. During this period, he also was a research fellow in Dr. Solomon Berson's laboratory at the Bronx Veterans Administration hospital. Following his residency, Dr. Gordis spent 10 years at New York City's Rockefeller University in the laboratory of Dr. Vincent Dole, conducting research in the areas of lipid metabolism, toxicology of carbon tetrachloride, analytical biochemistry of drug stereoisomers, the metabolism of alcohol and alcohol withdrawal. Subsequent to his tenure with Dr. Dole, Dr. Gordis founded the alcohol treatment program at the City Hospital Center at Elmhurst, New York, a large, comprehensive program with both inpatient and outpatient components serving some 15,000 patients during his tenure, and was Professor of Medicine at Mount Sinai School of Medicine. He has published on the clinical evaluation of alcoholism treatment, biological markers of drinking, disulfiram therapy, and the relationship between science and social policy.

As NIAAA Director, Dr. Gordis' principal goal is to continue support for activities designed to give maximum visibility to the Institute's role as a leader in alcohol-related research and the integral part of that role in preventing and treating alcohol abuse and alcoholism. This will include continued support for NIAAA's extramural and intramural research programs; support for a continuing Institute role in health professional education; increased attention to public policy research; and enhanced data collection and dissemination activities.

A member of Phi Beta Kappa, Dr. Gordis received his B.A. degree from Columbia University in 1950 and M.D. degree from the Columbia College of Physicians and Surgeons in 1954. He is a member of the Institute of Medicine of the National Academy of Sciences, the American Physiological Society, the American Federation for Clinical Research, Sigma Xi, the American Gastroenterological Association, and Fellow of the American College of Physicians.

THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Mr. SMITH. Dr. Gordis, your institute is 20 years old; is that right?

Dr. GORDIS. It will be 25 years old next year, Mr. Chairman.

Mr. SMITH. Twenty-five. I remember it when it was set up. And as you said, it accounts for more economic and social damage than all illegal drugs.

Dr. GORDIS. That is correct.

Mr. SMITH. In that 25 years, what have we gained on this problem?

Dr. GORDIS. I think we have gained, first of all, a change in attitude in the country. In many respects we have gained tremendous scientific insights on some very important features about alcohol use, and we have gained new therapies which I think are just the first step in what is going to be a new era.

As far as the social attitudes towards drinking, I think there have been tremendous changes in the way people view certain behaviors, such as drinking and driving. I think alcohol is being regarded seriously as a problem.

There are all sorts of public policy issues like age changes. The 21 year old drinking age, for example, which was established by Congress was in part in response to the scientific evidence that this would reduce the highway deaths among the young and, in general, the public is taking a more serious attitude towards alcohol in many respects than I think it had 20 years ago.

In the scientific arena of course we have had major advances in genetics. We know that there is a portion of vulnerability to becoming alcoholic which is inherited. We are learning much about the way alcohol affects the brain. And how the effects on the brain explain the way people do become addicted.

We are learning why some people become addicted while others who begin drinking never get into trouble at all. And finally we are developing a whole body of research which I think can influence the formation of rational social policy on alcohol questions as well.

Mr. SMITH. What we have here is that citizens don't want other people to drink if it is going to hurt them. But we say, go ahead and do anything you want, as long as it is just you.

And in the case of tobacco, it is the same way except that tobacco use has gone down.

Dr. GORDIS. Except among the young.

Mr. SMITH. People don't want to hurt themselves, in this country I am talking about. They don't want to hurt themselves, but they don't have the same attitude toward alcohol, do they?

Are we not getting the information out enough or what is wrong? Why can't we get people to understand that alcohol hurts them individually whether they are driving or not?

Dr. GORDIS. Mr. Chairman, I believe the information is out there. I think the public is much more responsive to it, but we must remember that alcohol, unlike the other drugs, is a legal substance in this country, and so there is all sorts of information——

Mr. SMITH. So is tobacco, but we are reducing the usage of tobacco substantially.

Dr. GORDIS. We are, except among the kids unfortunately, but in general you are right for the whole population.

The difference is of course that the effort to control tobacco did not happen overnight. It has been a 25-year history both of consciousness raising and of Congressional action, and the fact is that tobacco probably has no redeeming social qualities. It is certainly damaging to health, even in small doses.

The issue of alcohol is much more complex. First of all, it has a legitimate use. Second of all, there are some trade-offs as far as certain possible protective effects and the fact of the matter is that all the information that is available to the public on its risk is also counterbalanced of course by a tremendous encouragement to drink by the manufacturers, so we have a whole pool of information to which the public is subjected.

ALCOHOL ABUSE AND ALCOHOLISM

Mr. SMITH. I was a delegate twice to the World Health Organization with Congressman Laird when he was a Congressman. That was a long time ago, I don't remember what years they were.

At the World Health Organization they were very concerned way back then about alcohol use, especially in the case of France, for example, where they substituted wine for water because the water was so bad after World War II.

It seemed to me that they were more conscious of it way back then than we are now. Yet Europeans seem like they are not as conscious about tobacco harm as we are. You know something is not parallel here.

At the same time, in the last 25 years, that they become conscious about tobacco, you say they have become more conscious about alcohol. But we are getting greater results from the consciousness about tobacco than we are about alcohol, aren't we?

Dr. GORDIS. I think that is true. As I said, the alcohol issue is perhaps more complicated because unlike tobacco, there are pluses and minuses. The fact is that there is a legitimate use for it and many people drink it safely, which puts it into a somewhat different category.

SUDDEN INFANT DEATH SYNDROME

Mr. SMITH. Dr. Alexander, you mentioned Sudden Infant Death Syndrome. Is it better understood now than it was two or three years ago?

Dr. ALEXANDER. It is better understood. We have more information related to possible pathology, possible causes and possible means of prevention.

We have never had a handle on a way of prevention before. The research that has been done both in this country and elsewhere, stimulated in large part by the five-year SIDS plan that the Institute has developed, has contributed substantially to our knowledge, although we still don't understand the basic underlying mechanism.

There are some things that are starting to come together in the SIDS picture though. The brains of a number of infants that die of this show specific pathologic changes in the neurons in the centers that control sleep and arousal and responses to high levels of carbon dioxide in the blood or low oxygen.

There is also evidence that certain types of bedding, particularly soft bedding, are associated with an increased risk of SIDS, and now the information on sleep position in relation to SIDS has become quite clear. Studies both in the U.S. and in other countries have clearly shown that infants put to sleep on their stomachs have a higher risk of dying of SIDS than the infants put to sleep on their backs.

And soft bedding increases risk for SIDS only if infants are put to sleep on their stomachs, not in those that are put to sleep on their backs.

For this reason, we have worked with other Public Health Service agencies in putting together a public health information campaign that will be launched formally in June, trying to convey information to health providers through the American Academy of Pediatrics and nurses' groups so we can reach parents of all newborn infants in this country at the time they take their babies home from the nursery with the clear message that they should put their babies to sleep on their back rather than on their stomach, and that this is a way that they could reduce, although not completely eliminate, the risk of SIDS.

This will be a campaign that is orchestrated through the Surgeon General's office with her assistance in kicking it off. The American Academy of Pediatrics is involved along with a number of other major health organizations.

We have a behavior that should be very simple to change. It is not like we are telling people to stop smoking or modify their alcohol intake or sexual behavior or something, it is a very simple behavior. Put your baby down to sleep on its back rather than on its stomach, as our grandmothers did and our mothers did.

We also have access to the population. 99 percent of babies are born in hospitals and they get a discharge discussion with the doctor or a nurse at that time. We should be able to get that message to all parents about sleep position, and it is a very simple message, a very simple thing to do.

This campaign will be very intensively carried out over the next two years. We believe we can make a dent in the SIDS rate, and keeping in mind that SIDS is the leading contributor to infant mortality after one month of age, we should be able to help reduce its contribution to infant mortality and this country's high infant mortality rate.

Mr. SMITH. How many months are we talking here? What is the vulnerability?

Dr. ALEXANDER. The highest risk of Sudden Infant Death Syndrome is in the first six months of life, but it continues throughout the first year. It peaks at four months of life, and so we really believe that there is a developmental factor here a developmental change that does not occur in certain infants. What we also hope to be able to do through some other studies that we have going is identify the infants who are at higher risk for SIDS because of this developmental problem, and target them particularly for interventions, not just limited to putting them to sleep on their backs, but also to use some kind of monitoring device that will alert the parents if they do stop breathing for some reason.

Mr. SMITH. After a few months, the child turns over on its own.

Dr. ALEXANDER. That is right, at about six months.

Mr. SMITH. So it is not a matter of putting them to sleep. Do the ones that they start putting to sleep on their back, do they continue to sleep on their back?

Dr. ALEXANDER. For the first few months, yes, until they develop the ability to turn over.

Mr. SMITH. When they get the choice——

Dr. ALEXANDER. By then, the peak of incidence of SIDS has passed and you are on the declining edge of it. The back sleeping position is less important, but still significant.

Mr. SMITH. This is another area where we need to get out all the information we can because unfortunately it wasn't but a few years ago when some women were charged with murdering their child just because they didn't understand that there was such a problem.

Dr. ALEXANDER. That has been a major concern that a number of health agencies and the SIDS Alliance and others have tried to address by providing information not just to parents, but to health providers and the police force and others who investigate deaths like this, that this is an occurrence that does happen for unexplained reasons, and it is not child abuse or neglect usually on the part of the parent.

Mr. SMITH. Well, in the case of my children and grandchildren, all of them, if they didn't feel good, you put them on their stomach and it quieted them down. Why is that? Is that because it is more like the fetal position or what is it?

Dr. ALEXANDER. I really don't know the answer to that, Mr. Smith. One theory is that abdominal pain, stomach cramps, et cetera, are alleviated by pressure that is associated with placement on the abdomen, and if that is the contributor to the fussiness, whatever, it may help to alleviate it. What we are really suggesting, unless there is some indication to do otherwise, is that the babies be put down on their backs when you are putting them down to sleep.

Mr. SMITH. Thank you.

Mr. Porter.

Mr. PORTER. Thank you, Mr. Chairman.

Mr. Chairman, you and Dr. Alexander have just been talking about discovery or information and application, and we have often talked about the responsibility of NIH to go beyond discovery and apply the knowledge and at least bring it to the public in our country.

And I guess I wanted to go back and grind an ax that I have been grinding here about the lack of knowledge on the part of the American people and the lack of knowledge on the part of Members of Congress as to how important it is to fund biomedical research because of the payoff in terms of bringing down the costs of health care for the whole country in the future.

And I think that this book, as I have said for the last couple of days, is a very, very good start. But what I think I want to ask each of you and now Dr. Varmus maybe to end up, is what can we do to bring this message across and how important has it been in your institutes, how much savings have you been able to achieve—there isn't an entry, for example, Dr. Gordis in the book for NIAAA, and yet I can think of tremendous savings that have come out of knowledge in reference to alcohol abuse to society.

How do we bring this message across to people? What can you do as the developers and possessors of the body of knowledge in the area as to what it can mean to get your message across? I see you not only as the discoverers, but you have tremendous credibility and when you speak, people listen. So what can we do in each of your cases, and what can we do in an overall sense?

IMPLEMENTING RESEARCH RESULTS

Dr. ALEXANDER. There are various ways of implementing the findings from research. If it is a vaccine discovery, for example, such as the Hemophilus influenza program, it is a matter of doing the testing that demonstrates effectiveness of that vaccine, getting it licensed, and getting it recommended for use from the Academy of Pediatrics and the National Advisory Committee on Immunization Practices.

The Hemophilus influenza vaccine is one that is cited in that book as an extremely cost-effective advance from NIH research. The disease it prevents, influenza meningitis, was the leading cause of acquired mental retardation and deafness in the United States.

That disease is almost eliminated. It is vanishing from the scene in this country because of that vaccine. That is how a vaccine gets implemented.

Another is a screening program. Screening for congenital hypothyroidism—another cause of mental retardation that is completely preventable if you can detect it early enough—came from NICHD-supported research. It was implemented by legislation or by public health authorities in maternal and child health programs in each State such that now every infant born in the United States is screened for congenital hypothyroidism done by a blood test, from a heel-prick blood specimen.

Others are not quite so simple because they go to changing individual behaviors, whether it is smoking changes, sexual behavior changes, or whatever. Those are the more difficult messages to get across. A simple message in fact is the SIDS message that I was just describing. The message will be simple: Back to Sleep. That is the campaign slogan we will be using, put the baby on the back to sleep.

And so we hope that with the accessible target population, and a relatively simple behavior to change, we can get this finding from research into practice and application.

SAVING HEALTH CARE DOLLARS

Mr. PORTER. I want to go beyond that. I want to get it in the minds of the American people that it is saving health care dollars in the future and that because of the potential, proven potential of that savings that we need greater support for biomedical research.

I want to get the message out there as to how much you can save simply by putting money into research, learning things, and then applying them. That is what I am trying to reach.

Dr. Kupfer?

Dr. KUPFER. Mr. Porter, we at the Eye Institute have been grappling with this very question, because we have a very interesting situation. As a result of our clinical trials on diabetic retinopathy, we know that we can reduce rates of blindness from 50 percent to less than 5 percent. That is a very impressive result.

Yet, there have been two surveys done that indicate that only about 50 percent of the diabetic patients who are at high risk for blindness are actually being seen by an ophthalmologist and receiving treatment.

So here we have this incredibly good information and how do we get it to the diabetic population?

Well, thanks to the Congress, we now have a National Eye Health Education Program, and we are concentrating a certain amount of our efforts and energies on approaching the diabetes population directly, not through the physicians, but to the diabetic himself and herself, and telling them about the fact that they can go blind from diabetes. Interestingly enough, many of them do not know this—and that they can prevent this blindness with a relatively simple treatment that can be done in the ophthalmologist's office.

This program began about two years ago, and it is probably going to take another three years to begin to see a change in the behavior of the population. As you might expect, there is great concern on the part of patients that they might go blind and might have a serious disability. We must overcome that anxiety, that fear, that concern, and educate them that there is something that can be done.

Through the Eye Health Education Program, we are focusing on translating the results of the research into patient care, and that is not an easy thing to do, but it is absolutely essential.

We know that just treating 50 percent of the diabetics, we are saving between $1.2 and $1.6 billion a year. Just think of the additional savings, if we could reach more than just 50 percent.

DUODENAL ULCERS

Dr. GORDEN. At NIDDK, we had three examples in the book that you are referring to. One is related to, and I would like to emphasize this one in particular, the treatment of duodenal ulcer disease. One of the things we did was to bring about or catalyze the consensus. We used the NIH consensus development conference mechanism to do that because we now know that the role of bacteria in duodenal ulcers has been scientifically validated I think that is one of the greatest barriers to public dissemination of research results and utilization of this technology is lack of scientific validation.

We now know that it is a scientifically validated fact that a bacteria is intimately involved in the cause of duodenal ulcers. We don't understand all the ramifications of that. We know that treating that bacteria will prevent the chronic disease, that is, it will prevent one from having to take medications continuously. Since these are very expensive medications, the dollars we have listed in the booklet as there in cost savings are very large.

They take into account the complications of ulcers, such as bleeding and obstruction and other things that cause tremendous morbidity and need for hospitalization. One means to bring these research findings to the public is to catalyze the development of a professional consensus. In this case it is going to be through health professionals that I think we will have the biggest impact.

DIABETES CONTROL AND COMPLICATIONS TRIAL

The Diabetes Controlled and Complications Trial is very much analogous to what happened years ago with hypertension. Until we knew that mild hypertension was a major cause or complicating factor in cardiovascular disease and stroke, there was sort of a lackadaisical approach to managing blood pressure. I mean no one suffers from hypertension. The same is true for hypercholesterolemia. No one suffers from that. It isn't like a toothache that demands immediate attention. But once the important roles of high blood pressure and cholesterol were scientifically validated, careful management began. We now have added hyperglycemia, high blood sugar, to that list as a major public health issue. It will only matter because it has been scientifically and unequivocally validated, and everyone agrees about the impact of high blood sugar. I think this will have a tremendous effect on the health of diabetic patients.

We are going to have a major job in translating and disseminating these findings, but that job is certainly made much more plausible by the scientific validation. I think we now have a solid base from which to operate.

ALCOHOL INFORMATION DISSEMINATION

Dr. GORDIS. I think there is a both a narrow and wider response to your question, Mr. Porter.

There are some good signs. The very fact is that alcohol consumption is slightly going down over the last few years. In response to the Chairman's question, as the statement pointed out, the cost benefit research has actually been translated into the incorporation of treatment in the President's package.

As far as research dissemination goes, we responded to the congressional request for a triennial report on alcohol research called Alcohol and Health. Our brochure, which comes out four times a year, Alcohol Alert, goes to a mailing list of 40,000. We have a beautiful magazine for the general public called Alcohol Health World, which has a long list of subscribers.

We have a research database which is computerized and we publish monographs in both technical and nontechnical language. The media are interested in these topics. There were two relevant Washington Post articles which appeared recently. One was on clinical trials with naltrexone and one was about Fetal Alcohol Syndrome (FAS)

All of us among the directors are interviewed on the radio, especially on public broadcasting, on scientific issues, which is beneficial. Medical education in alcoholism which lagged behind is much better than it used to be. Alcohol is part of the curriculum in many schools today. It appears in board examinations and so on.

Now, optimistically, Research America conducted a recent poll in the last few years, but there was a funny contradiction within it. The respondents were all interested in research. They didn't really know what NIH was or what the NIH did I think a problem exists here which I think we are trying to address, but as you suggested it is far from solution.

There is a more general issue, too, about understanding research. This has to do with scientific illiteracy among young people. Until scientific literacy increases in the sense that people understand what research is all about and what it really means, there will be a continual problem of the kind that you raised, that is how to translate what research means into something that is eventually going to benefit the public.

So I think we have to work on many trends in this area.

Dr. VARMUS. Let me just pick up on some of the themes that Dr. Gordis was describing. All of our colleagues have given you examples in which their research has benefitted patients, and also affected cost savings in many cases, and described ways in which they are trying to get that information to the patients. However, I think your question addresses a somewhat different issue—that is, how do we convince the public and Congress that the investment in research has dividends, and that it is connected to health care. I think we also need to provide various forms of general education at all levels to make that point, including the type of public education Dr. Kupfer's Institute is carrying out at the moment over at Union Station.

I am amazed by your restraint, Carl, in not pointing that out. But many of my colleagues in academic institutions have been engaging in Public education regarding regarding the connection between research and health.

I think that some of the work that is being done through advances in genetics are particularly attractive vehicles for explaining how the study of our genetic inheritance is linked to assessment of risk, for example, in the case of colon cancer. Genetics is something that galvanizes the interest of young people. It helps them identify who they are, what their genetic endowment is, and allows them to see the connection between a fundamental science and their health. It raises important issues of moral and ethical qualities that engage the attention of almost everybody.

I am a little concerned about overemphasizing the simple dollar value of our research. There is no doubt that there are dollar values, but when you talk to sophisticated economists about some of the economic consequences of health research, one can get onto a slippery slope in which the prevention of a heart attack at the age of 60 can be seen not as a cost savings, but as an expense because that individual then goes on to develop the chronic diseases of old age.

It is not an argument I find very appealing because I think that the kind of work being done by Research America illustrates very clearly that the American public is willing to sacrifice a certain amount economically to have good health.

And I think we can show that in many instances we do produce cost savings. It is not always the case. But there is an important linkage between the science we do and the health of the Nation. That is the message we need to get across.

Mr. PORTER. I certainly agree that it can be overdone. But, and I hate to say this really in a certain way, but I think we need to get to the popular media. I think you need to be on Ted Koppel and

Larry King Live, and getting this message out there so that people have it between their ears and they have a positive feeling about support for the biomedical research because part of it is that science education problem. But then we need perhaps to do some remedial work at the adult age and really get a message out that NIH I think in the past has kind of shrunk from because they see that as not their role at all, and in a sense it isn't, but I think it is an institution that has such great credibility and you as director, not only in your position as director, but in your persona as a scientific researcher who is well known in this country, I think you would have a very good opportunity to get this message out and get people to understand it better, including Members of Congress, and build up the kind of support that I think we need to ensure strong support for our role as the world's greatest researchers, far in the lead of other countries, and have that secured in the future. That was my message.

Thank you, Mr. Chairman.

Dr. VARMUS. Thank you.

Mr. SMITH. Mrs. Lowey.

Mrs. LOWEY. Thank you, Mr. Chairman. I would like to associate myself with the remarks of my colleague, Mr. Porter.

Unfortunately the headlines focus on a whole lot of other issues rather than the NIH, and maybe we can all do our part in focusing more attention on the importance of biomedical research, and I wish it would make the headlines more.

JUVENILE DIABETES

But to proceed, Dr. Gorden, what can you tell the Committee about the Institute's support for new research on prevention of adult onset of juvenile diabetes?

Dr. GORDEN. Well, we have as a kind of a base for this the Diabetes Control and Complications Trial, which has demonstrated such unequivocal evidence for the efficacy of treatment of high blood sugar levels.

We have got a long way to go in ensuring how to give that treatment in the most effective way. So the tack we have taken is that high blood sugar is bad for you, and that it is the intensity and the duration of high blood sugar that leads to the complications in the eye and the kidney, and other systems.

We have taken two approaches. In the juvenile form or childhood form of diabetes, which we refer to as Type I diabetes, or insulin-dependent diabetes, we have inaugurated a prevention trial because we now understand that there is a window of opportunity during which we can recognize this disease before it becomes manifest in terms of high blood sugar.

We are utilizing that window of opportunity to use the most modern technology of immune modulation in an attempt to educate the immune system to prevent it from attacking the insulin-producing cells.

We have a clinical trial under way based on an enormous amount of animal work that precedes this and some very elegant basic science that gives us an insight into this. We have for a very long time had a major intramural program in Phoenix, Arizona studying the Pima Indians. This tribe of Indians has the highest prevalence of diabetes in the world. Over 50 percent of the members of this tribe after the age of 40 are diabetic. We have learned an enormous amount about the sequence of events that leads to this hyperglycemic state. Because of the work not just there, but in many other laboratories, we have learned much about the basic biology of how the system works with respect to insulin action, insulin resistance and related events.

This has allowed us to inaugurate a prevention trial. That is a trial in which we recognize the high-risk individuals who are likely to become diabetic and intervene at this very early stage to prevent progression of the disease.

The idea of both of these trials is that without a perfect methodology, we cannot completely prevent the hyperglycemia with the tools that we have available. However, we believe that we can prevent that event from occurring for five, ten, maybe fifteen years. If we can do that, then we can institute more effective ways to treat the hyperglycemia when it occurs, and we would have made an enormous impact on this disease.

NUTRITION RESEARCH COORDINATION

Mrs. LOWEY. Thank you. The budget justification mentions that the Nutrition Coordinating Committee is being transferred to the NIDDK pursuant to the NIH Revitalization Act.

What benefits do you expect from this transfer and will the transfer of this committee to one institute interfere at all with efforts to promote trans-NIH initiatives in nutrition?

Dr. GORDEN. We hope it will considerably enhance trans-NIH efforts in nutrition. Nutrition is a very broad-based area. It is really a discipline and not a disease, and needs and it really gains its momentum from multi-institute participation.

What we are trying to do is place the nutrition coordination effort in a more scientific context and to utilize that context as a springboard to gain the maximum effort of all institutes. The outside community is looking for a more central focus in nutrition while those of us at the scientific level understand that there are so many specific research areas that need to be applied to nutrition that we need all of the institutes' input into this.

Our challenge is to catalyze and bring together this meeting of scientific disciplines, and we are certainly willing to give it a try. We have designed a bionutrition initiative to have a central theme in order to demonstrate at least as a pilot experiment how this coordination works.

We believe that we can bring about a more consistent coordination with respect to other Public Health Service agencies, which are very important to this effort, such as, the Department of Agriculture, and other government agencies involved in nutrition research. We have a major effort in this regard under way at the present time, which we call the bionutrition initiative.

IOM REPORT ON NUTRITION RESEARCH

Mrs. LOWEY. I wonder if you can summarize for us briefly the major recommendations of the Institute of Medicine's report on opportunities in the nutrition and food sciences and how the institute plans to respond to these findings.

Dr. GORDEN. Some of the major concerns that they raised are related to training and bringing more interdisciplinary research into the nutrition field. That is something we are certainly going to address.

They are concerned about the initiation of more basic and fundamental research on issues of nutrient regulation, of gene expression, of antioxidants and vitamins, and many other things. They are very concerned about energy metabolism related to obesity.

With respect to this broad aspect of basic research in nutrition and with respect to training, those are the two issues that we are addressing first, and on which we feel that we can have the biggest impact initially. Later we can take up some of the other issues that they raised but we think that, for now, given all the restraints on administration, that this is the best approach to dealing with the issues.

We in fact supported very much that Institute of Medicine study. We brought together five institutes to allow that study to come about, so that the study in itself is an example of trans-NIH cooperation.

NATIONAL TASK FORCE ON PREVENTION AND TREATMENT OF OBESTY

Mrs. LOWEY. And can you outline for the committee the goals and activities of the National Task Force on the Prevention and Treatment of Obesity?

Dr. GORDEN. Yes. Obesity is a major health problem in this country. Because some issues have been raised about public dissemination of research results, particularly in the area of obesity where the public is getting mixed signals, we thought it would be useful to have a group of experts sift through this conflicting information and help us translate it into a coherent form.

OBESITY RESOURCE INFORMATION CENTER

We have established an Obesity Resource, Information Center in an attempt to disseminate the information that will be assimilated by this group of scientists. Having this group filter much of this information into the resource center is a valuable tool to translate and transmit the important things for the public to know. We will try to get rid of much of the myths and misinformation that are out in the community.

Nutrition probably is one of the areas that is most impacted from publicity in so many misdirected ways, certainly as much as anything else I can think of. The Obesity Resource Information Center is an attempt to try to make it right. We can't completely make it right, but we certainly can have an impact on it.

Mrs. LOWEY. This has been done before, isn't that correct? Or is this the first time that you tried to pull that all together?

Dr. GORDEN. This is the first time that we have tried to pull this together.

Mrs. LOWEY. And you are dealing with specific information or you are dealing with behavioral aspects of the issue as well?

Dr. GORDEN. Yes we are dealing with behavioral aspects. We have experts on this task force, behavioral experts, just as we have people who are geneticists. We also have people who are more biologically oriented, but people who are sound and whose judgment we respect enormously.

As Mr. Porter says, that just disseminating some of this information from the NIH can have an enormous effect.

COLORECTAL SCREENING

Mrs. LOWEY. Lastly, as you know, there is disagreement about the need to include colorectal screening in the national basic benefit package as part of health care reform.

The National Digestive Diseases Advisory Board officially favors the inclusion of colorectal cancer screening in the guaranteed benefits package.

What is the NIDDK's position on this issue?

Dr. GORDEN. Well, this is really a bit more of an issue for the National Cancer Institute. We don't have a specific official position. This is really something more in the realm of the National Cancer Institute.

I think this is a very important area. We now have tools for screening for colorectal cancer and the issue here is how we can most cost-effectively utilize those tools.

Mrs. LOWEY. Thank you very much.

Thank you, Mr. Chairman.

Mr. SMITH. Mrs. Bentley.

DRY EYE SYNDROME

Mrs. BENTLEY. Thank you, Mr. Chairman.

Dr. Kupfer, tell me about the dry eye syndrome.

Dr. KUPFER. The dry eye syndrome is just what it says. There is a lack of tears. The surface——

Mrs. BENTLEY. A lack of tears?

Dr. KUPFER. Yes, ma'am.

Mrs. BENTLEY. Not a tear continuously?

Dr. KUPFER. The dry eye is a lack of tears. There is the reverse situation where there is an excess production of tears, but in the public health arena, that is not as serious. It is a nuisance. It is annoying when tears roll down one's face, but the condition that really is a major public health problem is the dry eye condition where there is a lack of tears.

The surface of the eye must be kept moist at all times to wash away bacteria. Tears wash away foreign bodies and keep the surface of the eye smooth so that the eye can perform its proper activities in focusing light on the retina.

With the lack of tears, the surface of the eye begins to break down. This is painful. In fact it is one of the very, very few conditions in ophthalmology that is accompanied by pain. It degrades the vision of the patient and can lead to corneal ulceration and infection in some severe cases. It challenges the ability of the eye to continue to function. So it is a major problem.

Very often it occurs as a mild condition, that can treated adequately with artificial tears. More often it is associated with systemic disease, such as arthritis, and then it can be quite severe. In other cases it is associated with a group of problems with all of the secretory glands, such as those in the mouth, in the throat, as well as the lacrimal gland. And this is called Sjögren's Syndrome. That causes the severest form of dry eye and it can really degrade the integrity of the eye.

Mrs. BENTLEY. The reason I was asking is that I was told I had dry eye, but mine is tearing all the time, so it is not a dry eye.

Dr. KUPFER. I don't think so, ma'am. We would be glad to offer a second opinion if you would like to see us.

Mrs. BENTLEY. Well, I feel better.

Dr. KUPFER. I would mention that the dry eye situation does affect women predominantly. We have just recently held a workshop on this subject and we are now encouraging some research grants to be submitted for work in this area.

RETINITIS PIGMENTOSA

Mrs. BENTLEY. Now, tell me about the retinitis pigmentosa.

Dr. KUPFER. Retinitis pigmentosa is a degeneration of the retina which is inherited. It affects about 100,000 Americans. It unfortunately leads to blindness at the peak of the productivity of an individual, usually in their 30s, 40s, and sometimes in their 50s.

We are making major strides in retinitis pigmentosa, at the level of the basic laboratory research in which the genetic basis for the abnormality has been identified and hopefully will lead to clinical interventions.

Even more exciting has been the result of a clinical trial just concluded in the last six months to show that vitamin A given in the form of 20,000 units each day——

Mrs. BENTLEY. You have 15,000.

Dr. KUPFER. I am sorry. 15,000, you are correct. 15,000 units will slow down the rate with which the retina degenerates, so we now have at least an intervention that slows down the course of the disease.

Mrs. BENTLEY. Then you say that vitamin E does just the opposite?

Dr. KUPFER. Well, this is an interesting observation. The clinical trial was done with the idea that the patients would either receive vitamin A, vitamin E, a combination of vitamin A and E, or a placebo dose, in other words, just such a small amount that it wasn't really considered therapeutic.

And to everyone's surprise, although the vitamin A improved the condition of the retina in the sense it slowed down the degeneration, those on vitamin E actually showed an increase rate of change in the eye. Therefore, the advice has been for those taking vitamin E to stop and for those taking vitamin A to continue, and those who are not on vitamin A, to begin vitamin A under a physician's supervision.

Mrs. BENTLEY. I think that the fact that vitamin E may be speeding it up is a very important point and something that people need to know about because I have a number of friends who have retinitis pigmentosa, and I would like to bet that none of them have never heard about the value of vitamin E and A.

Dr. KUPFER. You are absolutely right, and of course we published a letter to all the ophthalmologists and optometrists concerning these results. We also have been working closely with the Retinitis Pigmentosa Association and of course they have been contacting patients and communicating this information to them.

ALCOHOL ABUSE AND ALCOHOLISM TRENDS

Mrs. BENTLEY. Dr. Gordis, on the subject of alcohol, I agree with you that there has been a change, but I wonder whether the decrease in the amount of alcohol consumed is due more because people are afraid of being arrested and put in jail than they are about the fact that they are concerned about their health?

Dr. GORDIS. Whenever there is a major social change which occurs over a decade or more, it is almost never the case that a single factor accounts for it, Mrs. Bentley, and I think the impetus to consider the penalties for drunk driving certainly accounts for part of the change.

I think the dissemination of some of the scientific features of our research is another part of it, and I think in general there are social changes and cultural attitudes which evolve independently of these two factors and play a role also I think all of these things happen at the same time.

Mrs. BENTLEY. Well, I won't prolong this, but I join in with what Mr. Porter had to say. We do need to get the word out to the public.

Thank you all for all your work.

Mr. SMITH. Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

GLAUCOMA

Dr. Kupfer, let me start with you. Let me also say what a pleasure it was to attend the event the other evening where the National Eye Institute was highlighted and the great work that they are doing, and so I would like to start with you.

The Institute's congressional justification that we have read here states that approximately 3 million Americans have glaucoma and as many as 120,000 are now blind from this disease. I also understand that African-Americans are affected disproportionately by glaucoma.

I wonder if we really know the actual extent of the problem in the African-American population, and if you would bring us up to date on the Institute's clinical trials of intervention to prevent or treat glaucoma.

Dr. KUPFER. I would be happy to, Mr. Stokes.

We now do have some very good information as a result of a study that was just done in the eastern part of Baltimore. In Baltimore's eastern health district about 5,500 individuals were examined, half being African-Americans, half being white Americans. The relative prevalence of glaucoma was estimated in these two groups, and basically we found that glaucoma is four to five times more common in African-Americans than in whites.

We are continuing this sort of comparison in other settings, but I think that estimate is going to hold. In terms of blindness, it is six times more prevalent among African-Americans. This is probably due to the fact that there is less access to health care amongst that group of citizens than one would like to see, and perhaps that is the reason why there is more blindness.

In terms of the clinical trials in glaucoma, there are several that have just begun and are now under way. The first is to study individuals who have not yet developed frank glaucoma, that is loss of visual function, but who do have elevated pressure in the eyes. These individuals are at high risk to go on to develop glaucoma and loss of visual function.

In this study, of course, as you might expect, a very large proportion of African-Americans will be included in the study population since this is a very high-risk group.

The second trial has to do with trying to answer the question of what the best treatment is for newly diagnosed glaucoma. Should we continue to give medicine and try to control pressure medically, or should we have as a primary intervention a surgical procedure which due to many, many research advances is much safer than it was two decades ago? Surgery may not only make unnecessary the continual use of medicine every day, but might even have a more beneficial effect on reducing the pressure in the eye and therefore retarding the progression of the disease. Again, this study will have a very large proportion of African-Americans.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. STOKES [presiding]. I understand that the National Eye Health Education Program, NEHEP, has been working with the National Medical Association, which is the professional organization for African-American physicians. I understand that the purpose of that effort is to try to reach minorities who are at high risk for glaucoma and diabetic eye disease.

Can you tell us a little bit about the relationship between the Institute and this group?

Dr. KUPFER. This has been a very, very productive interaction. We have worked with the National Medical Association in two communities. One is Durham, North Carolina and the other is Cleveland, Ohio.

In both settings there has been a major effort to educate the public. The public is the primary group that eye care professionals, various lay groups, such as the Lion's Club, and other community organizations are trying to reach. The effort is to convey to all African-Americans over 40 and all Americans over 60 the need for dilated eye examinations to detect glaucoma.

Half of all the people who probably have glaucoma are not aware of it. In addition, there is a high prevalence of complications from diabetes amongst African Americans and this is the other group that was targeted for eye health education in these two communities. This is part of the National Medical Association's Healthy People 2000, and we hope to continue to interact with that organization.

DIABETIC RETINOPATHY

Mr. STOKES. You mentioned diabetes and of course that brings to mind diabetic retinopathy. What progress are we making in that area, if any?

Dr. KUPFER. The results of three clinical trials done over the past 15 years has conclusively shown that if a diabetic will follow the recommendations arising from these clinical trials, the chances of becoming blind can be reduced from 50 percent in five years to less than 5 percent.

It is one of the most impressive results from any clinical trial ever done.

The sad part of this story is that we have not been able to adequately get the message out to the diabetic community so that they will seek eye care. We know from two separate studies that only about 50 percent of the diabetics who could profit from this treatment are actually receiving it.

Again, one of the major focuses of the NEHEP program is to educate the diabetic that diabetes can cause blindness, it can be prevented, but it requires a dilated eye examination by an eye care professional.

NUTRITION AND DISEASE PREVENTION

Mr. STOKES. Dr. Gorden, I have some questions to ask of you also. Dr. Gorden, we are learning more and more about the direct relationship between nutrition and disease prevention.

How extensive is the research in this area, in your Institute?

Dr. GORDEN. There are two aspects of this. One is the research that we are doing within NIDDK. Obviously obesity is a major concern of ours, because it is a major nutritional disorder. We have an extensive program related to the study of obesity at the very basic level and at a more clinical level. At our unit in Phoenix we have an extensive program studying energy metabolism. That is the mechanism by which the body, when imbalanced, utilizes energy and it eventually leads to obesity.

In addition, we have incorporated the division of Nutrition Research Coordination within the NIDDK, becoming the lead institute for nutrition in order to bring together the various aspects of nutrition research. For all of us at this table, nutrition has a major prevention role: in liver disease and alcoholism, in child health, in eye disease, and certainly in the broad areas that we have under the NIDDK purview. We have an extensive program looking into very basic areas of nutrition trying to understand the mechanisms by which nutrients affect various body functions. At the clinical level, each of us has programs that relate to our own specific areas.

The National Cancer Institute has extensive programs related to issues of cancer prevention, with respect to various foods. The whole issue of nutrient supplementation has been raised, and added to the issue of calcium supplementation.

In the field of child health, the issue of folic acid as a major preventive agent for spinal diseases in infants has arisen. So within the institutes there is a wide array of research that relates to nutrient intervention in prevention, and we certainly have only viewed the tip of the iceberg.

END-STAGE RENAL DISEASE

Mr. STOKES. I probably have time to get one more question asked before I, too, have to go and vote.

A few days ago, I visited an end-stage renal disease dialysis unit in my congressional district. What I saw there was really an enlightenment. It was also a very informative and educational experience.

How extensive a problem is kidney disease in our country? And, I might add that the ward I visited was almost 99 percent African-American.

Dr. GORDEN. Yes, it is a major problem in this country, Mr. Stokes. The Federal Government spends over $5 billion a year in Medicare costs for treating end-stage renal disease, and that is just the cost to the Federal Government.

There are upwards of 200,000 people affected who have end-stage renal disease. There are two major reasons why African-Americans seem to be disproportionately affected. The very interesting thing is that, although they have a higher rate of developing end-stage renal disease, once they develop it, they tend to do better than the general population. We don't understand the reasons for this, but the issue that we are facing now is understanding are why they have such a high prevalence.

Why do they have such a high incidence rate of end-stage renal disease? Diabetes is clearly one of the reasons. It is the leading cause of end-stage renal disease. African-Americans are affected at least one and a half times more than the general population and they are affected to an even larger extent by end-stage renal disease.

The other major issue is hypertension, and hypertension seems to affect African-Americans in a much more difficult way with respect to end-stage renal disease. We know that for African-Americans between the age of 24 and 44, the rate at which hypertension produces end-stage renal disease is at least 19-fold greater than for the rest of the population.

UNITED STATES RENAL DATA SYSTEM

These are things we have learned from the U.S. Renal Data System of the NIDDK, and we are instituting a major study in an attempt to interdict this disease. The pilot phase of the study has just come to completion, and we are going to make awards this fiscal year for a multi-center clinical trial. We expect to have at least 15 centers enrolled in the trial. Our preliminary data suggest to us that we can interdict this process. What we don't know is the very best way.

We have reason to believe that there are targeted blood pressures that are appropriate to African-Americans who are vulnerable to end-stage renal disease. We are going to test that hypothesis. We are going to test the question of whether drug A or drug B or drug C is more efficacious in preventing this, and within the next two or three years, I think we are going to have an enormous amount of information.

With what I have told you already about our diabetes research—that is the drug trial and the glucose trial and this trial—I very much hope that if you visit that center in the next couple of years that you will see a marked reduction in the number of African-Americans in that center.

Mr. STOKES. Thank you, Dr. Gorden. We will recess for just a few minutes.

[Recess.]

Mr. SMITH. Mr. Bonilla.

ARTIFICIAL PANCREAS

Mr. BONILLA. Dr. Gorden, I want to give you the opportunity to discuss, on the record, a recent study published in a British medical journal, the *Lancet*, that discussed an artificial pancreas and its effects on diabetes. I understand the NIDDK expressed strong reservations about the significance of the report.

What about that, Dr. Gorden?

Dr. GORDEN. There has been a recent paper discussing what is known as an implantable insulin pump. One might refer to it as an artificial pancreas. I am not certain if that is what you are referring to.

What is usually referred to as an artificial pancreas is an instrument that is not miniaturized, but is a relatively large instrument that does two things. It will sense the blood sugar level, through a chemical reaction, and then physically infuse insulin at a rate proportional to the blood sugar. This is of course the idealized pancreas. This is what the normal pancreas does and would be the ideal. This is only available for use in a hospital setting over a relatively short term because that equipment is not portable.

What I have a feeling we are talking about is the implantable pump. There have been a variety of pumps. Some are worn externally. They basically can infuse insulin on a continuous basis and be programmed to give a bolus. This is another version of that.

I wouldn't say that our view of the implantable pump is negative. I would say it is just not overwhelmingly positive in the sense there are not considerably greater efficacies for that device versus the externally worn devices or multiple injections as were used in our Diabetes Control and Complication Trial. It is possible that there is another study, but we certainly have not commented on it because I am not aware of it.

Mr. BONILLA. Okay. I am looking at an article here that I think is about four or five days old in a local newspaper, understanding that you always can't believe what you read in the newspaper, it says that the man succeeds—it is called an artificial pancreas in this article clearly.

"Man's success in experiment was described as a new technique that could herald a cure for Type I diabetes or insulin-dependent diabetes, IDDM."

So it clearly says that and if you would look into that, I would appreciate it.

Dr. GORDEN. Yes, sir, I certainly will.

[The information follows:]

TRANSPLANTATION OF ENCAPSULATED HUMAN ISLETS

Dr. Soon-Shiong's report in *The Lancet* deals with a major issue in the field of cell-based insulin replacement. It focuses on the development of strategies to protect transplanted islets or cell lines from destruction by the host's immune system, which can react to transplanted tissue as "foreign" and attack it. One approach to preserve the transplanted tissue from such destruction by the immune system is to create a physical barrier that protects the insulin-secreting cells. In this study, Dr. Soon-Shiong and his colleagues encased donor pancreatic inlets in a biocompatible semi-permeable membrane. The encapsulated human islets were injected within the stomach cavity in an insulin-dependent diabetic patient. Insulin secretion was noted within 24 hours post-transplant, and the patient remains insulin independent with excellent blood sugar control nine months after the procedure with no adverse reactions, including rejection. While this research is highly experimental and is not yet ready for general application, the results of this study in one patient are very encouraging.

Mr. BONILLA. Let me know because folks back home would be very interested in that.

DIABETES PREVENTION TRIALS

Could you discuss the $4.8 million study that was awarded in February to identify the genes that caused diabetes among many minorities?

Dr. GORDEN. We have a major effort to attempt to find genes that are important in noninsulin-dependent diabetes, that is usually referred to as the adult form.

If an individual has an identical twin who develops noninsulin-dependent diabetes, the other twin within five years has a 90 percent plus chance of developing diabetes. That, plus a variety of other studies, indicates that this is a genetic disease, a complex genetic disease, probably not due to a single gene in all likelihood as say diseases such as cystic fibrosis which are due to a single-gene defect.

Our problem is to try to identify the key genes, of which there might be many. We have launched programs in both insulin-dependent diabetes and noninsulin-dependent diabetes. We have a major research program in Phoenix. We have programs that also involve the University of Texas Center in San Antonio because in their case their major focus is on noninsulin-dependent diabetes.

We have found two different kinds of genes that are very important. One involves the genetic defects in the insulin receptor itself. We have characterized that in great detail in our laboratories in Bethesda. Our investigators have characterized a particular gene in something called Maturity Onset Diabetes of the Young which is a particular genetic form of diabetes, a gene that is in fact involved in sensing glucose. There is a lot of work going on there.

We have programs that are looking for particular so-called candidate genes, in other words, genes that are likely to be involved. There is an enormous screening program going on now plus programs that are using what are called positional cloning, that is the type of methodology in which you essentially search the entire genome in terms of trying to pinpoint a region that might specify diabetes.

So we are working in both directions. We are working from the point of view of the entire genome. We are working from the point of view of the so-called candidate genes which help us target this, and we hope that the intersection of these two different kinds of studies is going to help us to understand the cause of diabetes in both forms, that is the insulin-dependent form as well as the noninsulin-dependent form.

CLINICAL TRIALS BUDGET—NIDDK

Mr. BONILLA. Your requested budget increase is 3.7 percent and, as we have discussed with other institutes in prior hearings, that is below the inflation rate and in essence amounts to a cut.

What effect would the reduction in constant dollars have on new clinical trials affecting diabetes, obesity, end-stage renal disease, and other diseases?

Dr. GORDEN. Within that budget framework, we are launching a prevention trial for noninsulin-dependent diabetes. We are also launching a prevention trial for insulin-dependent diabetes, and we are launching a prevention trial with respect to hypertensive renal disease in African-Americans. We also have several smaller trials under way related to obesity.

All of these new trials are occurring because we were able to end the Diabetes Control and Complication Trial at least a year earlier than was projected. We have also just ended another trial called Modification of Diet in Renal Disease. We can only do these new trials by dovetailing them to previous programs. There is virtually no growth built into the system in terms of adding new programs, so essentially we have to wait until we can get one program terminated in order to get the other program started.

We have very little slack in terms of bridging these programs together. That has a major impact, but these new programs were given the very highest priority. Those that have the very highest priority are the ones that we are getting under way.

Mr. BONILLA. There is no question, though, if you needed to wave your magic wand, you would want more if there was more available, correct?

Dr. GORDEN. Absolutely.

Mr. BONILLA. Thank you, Dr. Gorden.

CLINICAL TRIALS BUDGET—NEI

A couple of questions for Dr. Kupfer, if I could. I would also like to ask you the same question that I asked Dr. Gorden, what current and future research areas would absorb in essence your cut that is proposed for you this year?

Dr. KUPFER. Perhaps we could just focus on the area of diabetes. I think we have heard from Dr. Gorden the very exciting results from the recent clinical trial which conclusively showed that controlling the level of blood sugar will reduce the incidence of complications.

However, one of the major complications of diabetes is retinopathy, and although it would be very good if every diabetic could control their blood sugar the way that the clinical trial managed to do it, I think from a very practical point of view this may not be as easy as one would wish.

Therefore, there should be other approaches to try to prevent the complications of diabetes.

We have been very interested in inhibiting a particular enzyme that seems to be involved with complications that develop, not only in the retina, but also in the kidney and in the nerves. We would want to expand considerably research activity in this area.

In fact we have been very fortunate that the Juvenile Diabetes Foundation has now concluded an agreement with the National Eye Institute to fund some of the research in this area. This is a research program area that I think could be expanded considerably and has great promise.

1–800 DIABETES PHONE LINE

Mr. BONILLA. I would like to let you know about a program in Texas that you may or may not have heard about that is called the

1–800 Diabetes Phone Line where anyone in Texas can call and request information ranging from recipes to treatment and prevention.

Are you aware of this type of program in Texas and, if so, does it sound like something that might be expanded to other States if they are not already doing it?

Dr. KUPFER. I think that is a very valuable program. In our National Eye Health Education program we would very much like to develop an 800 line that would allow individuals to phone in about the eye complications of diabetes. As yet, we have not been able to do that due to the financial resources necessary, which are considerable. I am very much in favor of this sort of approach. I think it is great that Texas has taken advantage of this opportunity.

I think the problem with diabetics is that, on the one hand, we have a very effective way of preventing complications in terms of blindness and yet the diabetics themselves do not realize that: A— diabetes can cause blindness, and B— that it can be prevented.

So this sort of communication with the public directly is very valuable.

Mr. BONILLA. Have you heard of this happening anyplace else?

Dr. KUPFER. I am not aware of this particular 1–800 number just being for diabetes, but the American Academy of Ophthalmology does have a national program where individuals who need eye care, and perhaps cannot have access to it, can call in and have the names of ophthalmologists who will see these patients without charge.

Mr. BONILLA. Okay. We would like to encourage that because it is working well in Texas and we are certainly going to do our part to try to publicize it as much as possible because it seems like half the battle is getting the word out.

Thank you very much for being here today.

Thank you.

Ms. DELAURO [presiding]. I suppose it is all good timing, but the Chairman will be back. As I understand it, he had to go off to a meeting and will be back shortly.

I wanted to just ask, Dr. Alexander, what was your slogan?

Dr. ALEXANDER. Back to Sleep.

Ms. DELAURO. I think we are going to hire you for our media campaign. It is short and it gets to the point.

But let me, Dr. Alexander, ask you one or two questions, if I might. Your budget justification states that several reports have been published during the past year that link ovarian cancer with the use of some drugs that are commonly used in fertility treatment to stimulate the ovary. And because so many women use these drugs NICHD is launching a study to determine whether fertility drugs increase the risk of ovarian cancer.

I am particularly concerned about this, not only because I am a survivor of ovarian cancer, but because of the problems that we are still trying to address with regard to the use of DES.

What are the drugs that are of concern here, and do you have any estimates as how many women have used or are still using them?

OVARIAN CANCER

Dr. ALEXANDER. The drugs that are used are ovulation-inducing drugs, either for direct induction of ovulation in patients who have patent tubes and have just ovulatory problems, or to induce ovulation for purposes of obtaining eggs—ripening eggs for in vitro fertilization (IVF).

And these are of particular concern because while in some instances women provide their own eggs, in other instances fertile women are being asked to serve as donors of eggs for others for in vitro fertilization. If there are risks with these drugs, and there is an associated risk of ovarian cancer they are being put at risk for some purpose that is not to their own benefit.

We have had a registry going following up women in ovulation-inducing protocols and IVF for infertility treatments, but none of the women in the study developed ovarian cancer. The numbers and length of followup are still too small to be definitive.

What we are doing is launching a new study in order to try and gain the population that is necessary to be able to get a definitive answer on whether women exposed to Pergonal or some of the other fertility drugs that are used, are at increased risk of ovarian or breast cancer, or whether there is in fact a problem at all.

Ms. DELAURO. You started to talk about the studies so that you are going to undertake a study to increase the number of women that you may be taking a look at.

What specific drugs are you going to study. You mentioned Pergonal.

Dr. ALEXANDER. I will have to supply the other for the record.

[The information follows:]

FERTILITY DRUGS AND CANCER

Drugs used for fertility enhancement are clomiphene citrate, chlorotrianisene, tamoxifen, human menopausal gonadotrophins, follicle stimulating hormone, luteinizing hormone, human chorionic gonadotropin, gonadotrophin-releasing hormone (GnRH), GnRH agonists, and bromocriptine.

Ms. DELAURO. In that context, you said the numbers are too few to——

Dr. ALEXANDER. We are dealing with 10 to 15 cases reported.

Ms. DELAURO. All right. Is the study ongoing? When is the study going to begin and how long might it take to get a sense of whether or not women in fact are being placed at an increased risk of ovarian cancer?

Dr. ALEXANDER. The new study obtains a larger sample and will take at least 5 years to compete. We also will be using our reproductive medicine network as a means of ascertaining this issue.

We are presently in the process of competing the reproductive medicine network that is studying people with infertility, to expand that to include other reproductive health problems, and also will be utilizing this population as a means of gathering additional information on the possible risk of ovarian cancer associated with these drugs.

Dr. Haseltine advises me that clomiphene citrate is the other drug for inducing ovulation.

Ms. DELAURO. Thank you. Dr. Haseltine, who is a good friend and neighbor in New Haven, Connecticut, I am delighted to see you here.

You talked about revising that study. How long is that going to take you to do? I am trying to get some sense of the time frame and when we are going to be looking at this issue.

Dr. ALEXANDER. The reproductive network is going to be completed this year for funding next year. The study itself, the other program that will be providing this information is a contract currently being negotiated, and is scheduled for funding in fiscal year 1994.

Ms. DELAURO. Tell me what level of resources will be committed to this study.

Dr. ALEXANDER. The reproductive medicine network will be increased from its current level of funding by approximately $2 million. I don't yet have a value for the contract level for the other study. Something in excess of $1 million.

Ms. DELAURO. Can you let us know?

Dr. ALEXANDER. I will be able to provide that. We don't have the final costs yet.

DANGER OF OVULATION INDUCING DRUGS

Ms. DELAURO. Tell me, are women being advised about the potential danger of the drugs?

Dr. ALEXANDER. The National Institutes of Helath and the Food and Drug Administration have met and worked together to determine what information needed to be provided, along with the American Fertility Society, and this information has been provided to the clinics that are treating women for infertility. There has not been a broad general public announcement about this.

We felt that the data were too preliminary to be alarmist at this particular stage. We have too few cases. We are not sure how reliable the information is and rather than put out a general public announcement that could be alarmist unnecessarily, we felt that we ought to be providing information to the care providers and also working through the drug companies that are providing these products so that they are informing the users through the package insert that these risks have been reported.

Ms. DELAURO. Well, let me ask the question. Should we stop using the drugs until we have satisfactorily answered the questions that have been raised.

Dr. ALEXANDER. Personally, I don't believe that we should. We don't have adequate substitutes for them at the present time. We need to be looking at possible alternative drugs for this purpose.

But I think the data are too preliminary at this stage to justify stopping their use. I think we need to be particularly careful with the issue of egg donors. The problem is this: The women who for the most part are undergoing these treatments, are women who have a problem to start with. The problem that is causing their infertility may also be a problem that is associated with an increased incidence of ovarian cancer.

And so we don't know whether this is something that is intrinsic to this population, or whether it is in fact associated with the drug use, and there just aren't enough cases yet to determine that. What we hope to do is increase the population sample study base so that we can follow enough drug-exposed and unexposed infertile women long enough to determine whether in fact there is an association with the drug use, or whether it is just an association with this particular population.

Ms. DELAURO. Well, I understand your reasons for not being alarmist. I appreciate that effort, which is why I asked my prior question of the length of time in terms of redesigning a study at the same time that women are continuing to take these drugs.

We all know what happened with regard to DES. We are still living with those effects. In terms of the provider community, I don't know that one can depend on them to get the information out to women about how at risk they may be in this area, so I am going to continue to ask, and I will work with the Food and Drug Administration as well to ask the questions about how long it is going to take for this study to be redesigned and is to be in effect so that we are in fact letting women know what dangers may befall them in this area.

I would also say with regard to the medical community, which is what I was thinking about when my colleague Mr. Porter asked his question in terms of research and getting information to the public, we didn't talk at all about the medical community and their getting the word out to people or being up to date about what the latest information is to be able to pass on that information.

I think that that is a missing piece. It has been this morning in the discussion, and it needs to be a critical piece of how you and others get the word out to the medical profession about the latest information, the latest research that in fact they can be passing on, and whether there is some way to monitor that effort.

BARRIER CONTRACEPTIVES

Let me ask another question, Dr. Alexander. Last year you may recall that I asked about the need for a barrier contraceptive facility to research and test new barrier contraceptives. You indicated that there was indeed a great need for such a facility, that it would lead to both cost savings and time savings in moving new products forward. There was also some discussion about the NICHD working with the FDA on new barrier contraceptive research.

I strongly believe that we need to move ahead in this area, particularly in the battle that we have against the transmission of HIV and sexually transmitted diseases. What is the status of your cooperative efforts with the FDA in this endeavor?

Dr. ALEXANDER. We are making arrangements for follow-up studies of the female condom. We also have studies planned with not only the barriers but with the spermicidal microbicides and that in fact is a specific targeted initiative in the President's fiscal year 1995 budget.

The barriers themselves are important, but we believe that the use of a microbicidal spermicide along with those barriers is of particular importance, and in fact the Institute will have an increase of almost $5 million in its efforts that go back about three years to push the development of improved spermicides that have microbicidal properties.

Ms. DELAURO. Is there—we did talk about a need for a facility. Is that a laboratory? Is there an effort under way to have a research facility? Is that being planned?

Dr. ALEXANDER. We had talked about that before. We are definitely pushing for improved testing facilities for contraceptives in general rather than having a specific one for barriers. We are establishing a network of Clinical sites for clinical trials to evaluate physical and chemical barrier methods to prevent pregnancy and STDs.

Ms. DELAURO. How much money is being looked at in terms of allowing that to happen?

Dr. ALEXANDER. I believe that contract is approximately $2 million per year.

Ms. DELAURO. What is the status of that contract?

Dr. ALEXANDER. The Request for Proposals has been developed. It will be issued during the current fiscal year.

Ms. DELAURO. How much money was spent on barrier contraceptive research in fiscal year 1993? The follow-up is how much will be spent in 1994, and how much do you anticipate spending in 1995?

Dr. ALEXANDER. The amount in fiscal year 1995 will increase to about $12.7 million. It is about $7 million in fiscal year 1994 and was $4.5 million in fiscal year 1993.

Dr. VARMUS. These figures are only for your Institute?

Dr. ALEXANDER. Just NICHD. The Allergy and Infectious Diseases Institute will also be part of this targeted new initiatives with another almost $5 million. That is on the topic of microbicides.

Dr. VARMUS. The total for fiscal year 1993, fiscal year 1994 and fiscal year 1995 for all of NIH is $9.2 million, $12.3 million, and $24.9 million respectively. Dr. Alexander's and Dr. Fauci's Institutes' provide the bulk of support for this research area.

Ms. DELAURO. Thank you. I think I have come to the end of my questions.

Mr. Porter.

Mr. PORTER. Thank you, Madam Chairman. I apologize to you. I had my other subcommittee meeting in the room next door. I am running back and forth between the two.

NIDDK EXTRAMURAL DIVISIONS

Dr. Gorden, could I ask about the funding allocations among your three divisions. How is that done?

Dr. GORDEN. We have three extramural divisions: diabetes, endocrinology, and metabolism; digestive diseases and nutrition; and kidney, urology and hematology.

Each division has a base of activities from a previous year's base and that base is carried forward. We try to do essentially two things. We try to take whatever incremental increase we have in our budget and add it in as equitable a way as possible to each of those programmatic divisions, as a percentage above its given base.

The other thing that we attempt to do is to bring together the so-called paylines among the divisions, so that the percentile grant payline is relatively consistent in all three divisions.

The third thing that we do is, of course, adhere to congressional directives that will tell us from time to time to do a specific thing that is related to one division. In that particular instance, that particular division then may receive an extra allocation of funds in order to carry out the directive.

Mr. PORTER. If you looked at the Division of Diabetes Endocrinology and Metabolism and you looked at its funding over the last three or four years, it looks as if the division received relatively low increases in relation to the other two divisions and in fact since 1988, its percentage has declined about two full points in terms of total funding.

I wonder, is that a strategic decision or simply a result of the factors you just mentioned, and do you expect this trend to continue in the future?

Dr. GORDEN. It in large part results from the third factor that I mentioned, that is, the directives for specific funding. Our goal is to try to take advantage of major opportunities, but we also have a goal, because of the size of the Institute, to try to maintain some constancy with the base. So we are attempting to keep the divisions at some sort of comparable level of support.

If you look over a very long period of time, for instance from five to ten years, I think you will find that the divisions very closely track with each other. Over any short interval of time, you may find some discrepancy with that, but that is mostly a function of the time period over which you look.

You will find in general a very close paralleling of the growth of these three divisions.

UROLOGY PROGRAM

Mr. PORTER. Can you tell us generally about your urology program, about prostate disease, and also about urological diseases in women? What progress is being made?

Dr. GORDEN. This is the program that has been the most rapidly growing in the Institute. It has grown almost 300 percent over the last five or six years. And that has largely been fueled by initiatives that are related to prostate disease, both benign prostate disease and collaboration with NCI related to prostate cancer. These two areas sort of closely track each other in terms of the kind of research that they are doing.

The other major growth area has been bladder diseases, particularly related to urologic diseases of women.

The women's initiative has played a major role in diseases such as interstitial cystitis and other related disorders. That program has grown to about $8.5 million over the last few years from an extremely small base of under $1 million.

So here are examples of urology programs that in a collective sense have grown to about $35 million from the very, very small base. This growth represents about a 300 percent change for the Urology Program.

These changes have been largely related to both Congressional directives and Institute initiatives in terms of trying to address what really are major, major health problems within the purview of urology, and in trying to strengthen urology as a fundamental science.

Urology did not have the kind of scientific base that we have in many of the other areas of NIDDK research. We needed to develop that field, and then we had an avenue through which we could add more resources. I think it is a very good example of developing a field, both from a basic point of view and a clinical point of view, and then utilizing those resources in a much more effective way.

POLYCYSTIC KIDNEY DISEASE

Mr. PORTER. Dr. Gorden, in today's Washington Post, there is an article on polycystic kidney disease and the use of Taxol. Can you tell us about that?

Dr. GORDEN. Yes. This is again another example of trying to understand and override a genetic disease. We believe there are going to be many examples like this for which we will find pharmacologic means of overriding the genetic defect before we can actually replace the defective gene. Although this is a good example, in an experimental sense, it is not something that has clinical application. Taxol seems to affect a cell known as the cytoskeleton, the part of the cell that gives it its fabric, and this effect seems to inhibit cyst formation.

If you inhibit this system at a particular stage in mice that are genetically prone to develop cystic disease of the kidney, they will be protected from developing the disease over a prolonged period of time.

That is a very new concept because it has not been part of the repertoire of thinking about this disease. Scientists had focused in a number of other areas, both from a genetic point of view and the point of view of the mechanism of cyst formation. This is an important new concept and we hope to use it in potential therapeutic strategies that may be more relevant for patients.

This is a very important genetic disease affecting over half a million Americans and is a major cause of end-stage renal disease. It frequently does not manifest itself by causing end-stage renal disease until a person is in his or her 40s, maybe older. But this is a very important observation, very recently published, as you mentioned.

Mr. PORTER. Dr. Alexander. I understand that the National Center for Medical Rehabilitation Research is interested in establishing centers of excellence for medical rehabilitation research. These centers would perform outcome studies, provide training, develop improved measurement techniques, and conduct other crosscutting rehabilitation research.

How would these centers differ from existing centers and other disability-related research, particularly at the Department of Education?

MEDICAL REHABILITATION RESEARCH CENTERS

Dr. ALEXANDER. These centers have been discussed and proposed by our National Advisory Board on Medical Rehabilitation Research. They particularly would focus on some of the emphasis areas in the plan developed by the Board for Medical Rehabilitation Research.

They would focus thus on improving functional mobility, understanding behavioral adaptation to loss of function, examining body system responses to physical impairments, and facilitating useful functioning by applying new technology.

The centers that are supported by the National Institute on Disability and Rehabilitation Research tend to focus on just one specific area. There will be a spinal cord center, or a head injury center or whatever.

These centers would be designed to be much more integrated. They would put together a mix of projects that in the aggregate would address all the key concepts there are, through physiology or impairment or functional status or even focusing to a large extent on transfer of research generated information to medical rehabilitation practice and research, as well as looking at measurement issues, which are a real problem in the field, and to treatment effectiveness research.

So these are areas that are not really being addressed by the National Institute on Disability and Rehabilitation Research in the Department of Education and they would be different in their focus.

Mr. PORTER. Thank you.

Has funding for the contraceptive and infertility research centers been sufficient to conduct both basic research and perform the clinical trials necessary for the approval of a new method?

CONTRACEPTIVE DEVELOPMENT AND INFERTILITY CENTERS

Dr. ALEXANDER. The centers have not been able to be funded at their planned and intended levels. They are funded at a level that enables them to pursue their basic research in product development, but their funding to this stage has not really enabled them to engage in the clinical trials that were envisioned for them at their formation. Only in a very limited way have they been able to do so. The fiscal year 1995 budget adds $1 million to those centers for clinical trial initiation.

Mr. PORTER. Is that enough money?

Dr. ALEXANDER. It can get them started. It will not be able to meet the desired numbers of clinical trials or the scope of population that they envision being able to recruit in fiscal year 1995, and the one trial would be focused in the topical microbicide area where the initiative is being added.

Mr. PORTER. If you could get what you needed in this area, what would you ask for?

Dr. ALEXANDER. The cost for full conduct of the clinical trials and the basic research that could be mounted in those centers this year would be approximately an additional $4 million.

Mr. PORTER. And has NICHD been able to institute the loan repayment program to these centers to help attract young researchers in the field?

Dr. ALEXANDER. We have not implemented it this fiscal year. We have initiated the efforts in discussions to plan to implement that in fiscal year 1995.

Part of the problem is determining the mechanism that would be used for making these funds available and some of the administrative problems associated with that. But we have started the effort.

It will be built much along the guidelines that the AIDS loan repayment program has operated within the intramural side, and we would hope that our initial efforts will be in the contraceptive and infertility research centers; on the extramural side starting in fiscal year 1995.

Mr. PORTER. Madam Chairman, I have just two more questions. May I?

Ms. DELAURO. Yes, of course.

NEI GENE THERAPY

Mr. PORTER. Dr. Kupfer, what are the prospects for effective gene therapy for eye disease, and how important is the genome center to the National Eye Institute?

Dr. KUPFER. We have some very unique opportunities in gene therapy for eye disease. First of all, there are many diseases of the cornea, and since that is accessible so easily, one can visualize the introduction of normal genes directly onto the cornea, very much the way that the cystic fibrosis problem is being approached by aerosol into the lung pathways.

There is a very active program going on in the intramural program of the Eye Institute to approach a particular type of retinal degeneration with gene therapy. I would predict in the next five years, we are going to see some early clinical trials of this intervention.

The whole area of retinitis pigmentosa is opening up very quickly in terms of which genes are abnormal, and I think there are strategies that are being developed on how to introduce normal cells into the retina to take up the functions that the abnormal cells are unable to carry out.

We want very much to collaborate with the human genome program. Fortunately, when Dr. Collins came from the University of Michigan, there was a very active program in glaucoma genetics at that institution, and we hope to continue that collaboration with them and broaden our areas of the collaboration.

Mr. PORTER. Thank you.

ALCOHOL USE TRENDS

Dr. Gordis, what effect has the—this is not a scientific question, I guess. I am wondering about what effect has the encouragement of the use of alcohol by older people, what effect has that had on rationalizing the use of alcohol by younger people?

It seems in the last four or five years it has become acceptable, in fact encouraged for older people perhaps to have a drink a day. It was even mentioned I think in the last Wellness newsletter of the University of California at Berkeley as one of the things that it suggested. But doesn't that also encourage young people to rationalize that it must therefore be an acceptable thing for them to get into and perhaps not in a moderate way?

Dr. GORDIS. I think that is probably one influence. The whole issue of the wellness push is a very complex one, as obviously you know, Mr. Porter. There are trade-offs in all decisions about drinking.

The evidence that there may be some protective effect against coronary disease is probably correct for one or two drinks a day in males and maybe a little less in females.

The popular push on this topic now neglects the fact that every decision to drink involves trade-offs. For the teenager, the issue is not eventual heart disease, it is interference with school work, and risk of death on the highway. For the elderly person, if he has lived to be 75, perhaps he is not going to die of heart disease the next day, but there are risks of drug interactions and falls and other kinds of injuries.

There is some complexity because there are trade-offs in terms of possible coronary protection on one hand. Yet there are risks of hypertension, susceptibility to addiction, and certainly damage to the fetus during pregnancy, when one shouldn't drink at all.

The rush to encourage a uniform drinking standard for adults on the grounds of wellness I think is premature, although there is a complex question here.

The influences on youthful drinking, though, are so diverse aside from that issue, that I think one doesn't have to look only to the wellness push that is aimed at adults to account for the increases in young drinkers. There are many other forces encouraging that, which I think you know as well as I do.

Mr. PORTER. Thank you, Dr. Gordis.

Thank you, Madam Chair.

Ms. DELAURO. Thank you.

Mr. Stokes.

INFANT MORTALITY

Mr. STOKES. Thank you, Madam Chair.

Dr. Alexander, let me start with a subject that you and I have discussed for a number of years now, and that is the subject of infant mortality. This is an area in which countries are ranked. Where does the United States now find itself ranking?

Dr. ALEXANDER. We still find ourselves approximately 23rd depending on what you count as a country and what particular years you take, but 23rd is about right.

Mr. STOKES. What does this ranking of 23 mean?

Dr. ALEXANDER. That means that we are doing far less well than we should be by our children in this country. It means that many other countries are making better investments in their children, in the prenatal care given to women, that they are applying what they know better than we do, and that we ought to be making better strides than we are.

It also means that we have a different population, a more diverse population, and a more difficult population to reach. Infant mortality is higher in rural areas than in more urban areas except for inner-cities. It is considerably higher as you well know in African-American populations. It is somewhat higher in Hispanic populations, but the Hispanics actually do relatively well, depending on which segment of the Hispanic population you look at.

We have made considerable strides. When this Institute was started, our infant mortality rate was over 20 per 1,000 births. It is now down to about 8.2, but the black-white discrepancy remains more than two to one.

We do, in many areas, take care of pregnant women and newborn infants in a way that our infant mortality is quite respectable. If you look at the difference among States, New Hampshire and Maine would rank second in the world only to Japan in their infant mortality rates, but other places, such as Mississippi, the District of Columbia, the story is quite different and gets close to the rankings of lesser developed countries.

Much of the advance that has been made in improving infant mortality has come from research. The introduction of surfactant as a result of the NICHD and NHLBI research in the last several years has taken, more than a whole point off our Nation's infant mortality rate. That is a 10 percent reduction in just three years. So we are making progress.

We need to continue that effort and particularly focus on the low birth weight infant. Our problem is not so much in keeping the low birth weight infant alive as in reducing the number of low birth weight infants that we have to care for. And that is where the Institute is making major efforts both in the intramural program and the extramural program.

The new perinatal research branch in the District of Columbia that Dr. Roberto Romero is heading will be conducting both a laboratory and clinical program of research focusing largely on the African-American population in the District, looking particularly at prevention of low birth weight.

The research projects that we support are often directed towards finding ways of reducing the problem of the incidence of low birth weight.

INFANT MORTALITY—PROGRESS

Mr. STOKES. In light of what you are telling us, what else do we need to do to make the kind of progress that needs to be made?

In the U.S., we still have a tremendous disparity between the rate of infant mortality for African-Americans and for white Americans. Aditionally, while we are making progress, we are still 23rd in the world. The United States is the most developed, and the richest country in the world.

Are we building into your Institute's budget the kind of opportunities needed to reduce this disparity?

Dr. ALEXANDER. We are clearly making substantial efforts and those efforts increase each year. There are limitations. The perinatal research branch that I mentioned to you that will be in the District working in collaboration with Georgetown, with Howard University, and D.C. General Hospital, shows only minor growth in fiscal year 1995 compared to the targeted major growth that was anticipated when the contract for support of that branch was awarded to Georgetown last year.

The clinical trials efforts in the networks of maternal-fetal medicine units and neonatal intensive care units are basically static and will be able to increase and only add a new trial only when one drops out. Other clinical trials are supported by contracts.

We have, for example, a study of supplementing calcium to pregnant women as a means of trying to reduce preeclampsia and reduce the problem of low birth weight, again a problem that is particularly prevalent among African-Americans.

That trial has had increased costs associated with it. We are meeting those costs, but it means that other studies don't get started.

SUDDEN INFANT DEATH SYNDROME (SIDS)

Mr. STOKES. Let me ask you about another disease or problem. This is one that has to be one of the most traumatic to any family in America and that is sudden infant death syndrome. How extensive a problem is SIDS?

Dr. ALEXANDER. It is still a problem. The numbers are still high, running close to 6,000 deaths a year. It is still the leading cause of infant death, infant mortality after one month of age.

About 16 percent of our infant deaths are due to SIDS. We do think we have leads on ways to reduce that number. We still don't know the basic cause. We do have a picture that is starting to come together of developmental problems creating a susceptible population of infants with SIDS clearly associated with sleep position.

I have mentioned this campaign that we will be launching through the Public Health Service to have infants placed for sleep on their backs as opposed to on their stomachs, which we think can make substantial inroads into the problem of SIDS.

It is not going to make it go away, but we think it can cut SIDS by somewhere between a quarter and a half based on the experience of other countries that have implemented programs like this.

We will also be making efforts to try and identify a population that is at increased risk. We want a screening test, if you will, for infants who would be more susceptible to SIDS and would be candidates for more close monitoring with electronic apnea monitors.

We have a major clinical study, the CHIME study, involving five different sites that will be testing this whole new generation of apnea monitors both for its effectiveness as well as whether in fact there is a pattern in these infants that allows us to select out a vulnerable and susceptible population you could target this to.

UNIQUENESS OF ALCOHOL RESEARCH

Mr. STOKES. Dr. Gordis, yesterday we received testimony from Dr. Leshner of NIDA. During my questioning of him, it was indicated that the United States is the most drug addicted, drug abusive, drug dependent Nation in the world.

This is obviously a problem and major concern of your Institute.

Does your Institute, NIAAA, interact with NIDA in terms of the drug abuse problem?

Dr. GORDIS. There are similarities and there are differences, Mr. Stokes. The similarities are that in certain areas of basic science, there may be certain commonalities in neuromechanisms having to do with addiction, and there are some differences which time does not allow the details to be enlarged upon now. Move than any illegal drug, alcohol damages the body pervasively.

I think from the point of view of the public health aspects of your question, we are dealing with in many ways two different worlds. In the case of the illegal drugs, we are dealing with substances which are illegal, which are connected with the criminal justice system with interdiction, and a number of areas outside of the science of NIDA, which are very much germane to that topic.

In the case of alcohol, we have a legal substance which is governed in its use by various laws and regulations. Other agencies such as the Bureau of Alcohol Tobacco, and Firearms have a role in how alcohol is distributed and sold. It is a legal substance which most people use without any trouble.

A minority get into trouble with it and the issues that surround the alcohol public health side are very different than those of the illegal drugs.

They have to do with where in the whole spectrum from total freedom of use to total regulation, we want to position the country How much do we want to control things, such as the price, which are related to consumption and its complications?

We have regulations dealing with the age at which it can be sold, and its impact on driving. What about the impact on cirrhosis, death rates, and the whole study of the question of the impact of advertising, health warning labels, etc.?

Therefore, we have a whole world of science having to do with public policy and medical consequences, which makes these two spheres distinct. We have had collaborative activity with NIDA in several areas in which the collaboration is very much germane.

We have collaborated with them, for example, on various social issues in connection with the substance abuse and Mental Health Services and so on, but in administration the public policy arena, I think we are in many ways in two different worlds. This is not so much the case in the area of neuroscience.

FETAL ALCOHOL SYNDROME

Mr. STOKES. Your justification states that despite a decline in drinking during pregnancy, fetal alcohol syndrome remains the leading preventable cause of mental impairment. The incidence is estimated to be in one to three infants per 1,000 live births. To what extent has research yielded answers to this problem?

Dr. GORDIS. As you know, Mr. Stokes, the definition of the problem and its elaboration were the product of NIAAA research about 20 years ago. And during that time a variety of research has been conducted to understand how it occurs, what the patterns of drinking are which lead to the fetal alcohol syndrome, and hopefully what might reverse it or prevent it even if the drinking were to occur.

In addition, there is research on better detection of drinking in pregnant women to hope to prevent it in the first place.

The main avenues of research which we have been looking into in relation to its cause have several chapter headings, which I will just name. We are looking at the issue of nutritional transport across the placenta. We are looking at the issue of the impact of alcohol on brain cell growth in the pruning of the nervous system in its orderly development during embryogenesis. We are examining the impact of alcohol on certain substances called morphogens which have to do with the determination of how digits and arms, for example, are formed. We are studying the impact of alcohol on the immune function in the fetus.

Thus in a wide range of research, we are working to understand how alcohol interferes with the orderly body formation, and how in lower doses it leads to a condition without the morphological abnormalities, but rather with subtle differences of intellectual and developmental stages that may persist into the teen years and beyond.

I think we have made significant progress and on the clinical end, we have increased our ability to detect drinking during pregnancy by a variety of interview and chemical tests.

In addition, we are also examining the possibility that certain groups—for example, African Americans which seem to have a higher incidence of fetal alcohol syndrome—may have certain susceptibilities which go beyond the social and economic discrepancies between the two groups.

There is a possibility that because several different genes which affect alcohol metabolism may be more common in certain ethnic groups than in others, the fetuses of mothers and fathers in these groups may be somewhat more at risk for the fetal alcohol syndrome. This is an avenue of research which is also being pursued.

Mr. STOKES. Thank you, Dr. Gordis.

Thank you, Madam Chair.

Ms. DELAURO. Thank you.

POLYCYSTIC KIDNEY DISEASE

Dr. Gorden, let me follow up if I might with one or two questions on polycystic kidney disease. Approximately how many researchers are working in your agency on grants that deal with this?

Dr. GORDEN. We have approximately 30 active project grants in the area of polycystic kidney disease. That actually doesn't include all the people that work in the related areas such as studies of the so-called microfilamentus or tubular system. Many other people are working on very basic aspects of polycystic kidney disease, so we would say that this is another community that started several years ago with a very, very low research base.

Now, we have a research base directly related to that disease of something in the neighborhood of $5 to $6 million, and some very important events have occurred in the field over the last several years.

We are very encouraged. We have some animal models. We have research leads now into how we should be approaching this important genetic disease, the most important genetic disease of the kidney.

Ms. DELAURO. That is what I understand. How does that funding compare to other genetic diseases such as cystic fibrosis? What is the comparison?

Dr. GORDEN. It is not as great as cystic fibrosis. I would like to see it become as great, and I would like to think it could become as great if we can reach a critical threshold as we have done in cystic fibrosis. In 1989, as you know, our Institute supported the research that elucidated the cystic fibrosis gene, and that has caused a enormous explosion of research in that field.

We have a tremendous obligation to follow those opportunities. Because of that, we would like to make that kind of initial breakthrough in polycystic kidney disease so that we could follow the same kinds of exciting leads as we have done in cystic fibrosis.

Ms. DELAURO. You said that polycystic kidney disease affects more people than almost any other chronic genetic disease. The Federal Government winds up paying the cost of the dialysis, winds up paying the costs for transplant for PKD patients.

Wouldn't it be a good investment to increase the amount of funding we have in that area to take a look at this disease and the impact it is having in the long term in order to achieve the cost savings?

Dr. GORDEN. I certainly agree, yes.

ALCOHOL AS THE NATION'S NUMBER ONE DRUG OF ABUSE

Ms. DELAURO. I take it you agree.

Dr. Gordis, let me just ask you one or two questions. In the past few weeks we have seen some serious reports, quite frankly to me disturbing reports, about the increase in drug use and a decrease in the concern that Americans have about occasional drug use.

In terms of alcohol abuse, is it your view or is this considered any kind of a gateway into drug abuse, particularly as it has to do with young people today?

Dr. GORDIS. In most instances, but not invariably, there seems to be a common sequence in which various substances which are mood altering are used by adolescents, and alcohol is usually among the first and tobacco likewise, and then frequently the classic series is marijuana, then cocaine and heroin. That is not always so. There are places especially in the inner cities, where the cocaine use occurs fairly early.

The word "gateway" is often used as if alcohol were merely unlocking the door, as if the real trouble were beyond. I would like to emphasize that alcohol itself is overwhelmingly the real problem. This is what causes the youngsters to die on the highway or neglect their education. This is causing the fetal alcohol syndrome, something we have talked about before, and even the behavioral results of alcohol yes can have some effect on the acquisition, for example, of HIV.

As far as the damage that alcohol causes, the word "gateway" tends to minimize it and sees it simply as the doorway to the problems, while I believe the actual facts speak for themselves, that is the alcohol itself is the major problem among all drugs of abuse in this country.

Ms. DELAURO. Are you, Dr. Gordis, participating in the studies that NICHD recently announced to take a look at what influences contribute to the development of behaviors in adolescents that affect health, including alcohol?

Dr. GORDIS. Within the last few weeks, as a matter of fact, Dr. Alexander informed us of his Institute's plans on this, and we are now having conversations on how we can participate.

Ms. DELAURO. You are going to participate in that effort. What other studies are you supporting on the factors that lead to alcohol abuse in adolescents and how we might be able to prevent this?

Dr. GORDIS. That is a very big question, Ms. DeLauro. Our studies on vulnerability really are of two separate kinds.

One area is the genetic vulnerability for which we have massive evidence in twin and adoption studies. This has led to our present cooperative study on the genetics of alcoholism which is being conducted in six centers now. Cases are being interviewed, DNA is being acquired, and the various techniques of linkage analysis are being applied to find those genes which are responsible for that portion of the vulnerability which is inherited.

But a great deal of alcoholism, perhaps most of it, is not genetics. A variety of other influences apply, including availability, peer pressure, and stages in adolescence having to do with arousal and so further researchers are studying those influences intensively in many settings, both on the basis of the individual adolescents and the communities involved.

One of our research centers is devoted to precisely to that topic, that is the effect of alcohol in adolescence and the risk factors that have to do with the vulnerability of adolescents to alcohol abuse and alcoholism. And we would be very happy to amplify the answer to this for the record.

[The information follows:]

RESEARCH CENTER ON ALCOHOL AND ADOLESCENCE

Investigations are being conducted to determine the co-variation between alcohol beverage consumption by adolescents and biological maturation; and to elucidate the factors associated with the vulnerability to develop medical consequences, especially liver disease and nutritional deficiency, as a result of excessive alcoholic beverage consumption. Researchers are also working to clarify the association between alcohol abuse in adolescents and cognitive impairment and to identify and characterize the basic patterns of alcohol use disorder in adolescents. Studies are also seeking to ascertain the association between alcohol use disorder in adolescents and precedent, concomitant, and long-term psychiatric morbidity.

Ms. DELAURO. Thank you very much. Those are all the questions I have. The committee will adjourn until 2 o'clock this afternoon. Thank you very much for your testimony.

[The following questions were submitted to be answered for the record:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

PERINATAL RESEARCH BRANCH

Mr. Smith: Tell us more about your new Intramural Perinatal Research Branch in the District of Columbia. Which institutions are participating and how many staff are allocated to the project?

Dr. Alexander: The Perinatal Research Branch was established in the NICHD subsequent to House report language on the FY 1992 Appropriations Bill which provided support for "...the establishment of a...comprehensive...obstetrical research program...as an off-campus branch of the Institute's intramural program..." The Branch's mission was to address the relatively high rate of infant mortality among African Americans. The Branch will be located at Georgetown University, the focus of a consortium which includes Howard University, DC General Hospital, as well as other major health care providers in the District of Columbia. The Branch is led by Dr. Roberto Romero, currently employed by the Institute under an Intergovernmental Personnel Act (IPA) agreement with Wayne State University. The Branch currently supports four research fellows and an additional 10 employees supported under the contract with Georgetown University.

Mr. Smith: What major research areas has the Intramural Program targeted for study?

Dr. Alexander: The major areas of research that have been targeted are prenatal diagnosis, with particular emphasis on fetal surgery, and prevention of premature delivery.

Mr. Smith: Is the program funded entirely from your budget or does the Office of Research on Minority Health provide some financial support?

Dr. Alexander: Funding for the Perinatal Research Branch in FY 1994 and FY 1995 comes entirely from the NICHD budget.

D.C. INFANT MORTALITY RESEARCH INITIATIVE

Mr. Smith: With funding from the Minority Health Office, you are supporting a community clinical trial in the District of Columbia relating to infant mortality. Is the trial underway, and what interventions is it testing?

Dr. Alexander: The studies are ending their planning stages and the initial protocols will be implemented early this summer. They will be examining the feasibility of interventions to increase participation in early prenatal care, studying the relative impact of illicit drug use and other factors occurring with illicit drug use on infant outcomes, examining the effect of levels of perinatal care services on infant outcome, and attempting to improve parenting skills.

SURVEY OF ADOLESCENT HEALTH

Mr. Smith: Tell us more about your longitudinal adolescent health survey. What are the major elements of its design, and why are you confident that the survey will collect accurate information?

Dr. Alexander: The ADD HEALTH study responds to a congressional directive for a comprehensive, national study of the determinants of adolescent health and health behavior at the individual and community levels. This innovative study will investigate the impact of the adolescent's social and physical environment - the family, peer group, school, neighborhood and community - on health behaviors and health outcomes.

The study begins with a sample of 160 middle and high schools nationwide. Features include a short questionnaire completed by all 160,000 students attending grades 7-12 in the sampled schools, and detailed interviews conducted in the home with over 19,000 adolescents and parents. Parental consent will be obtained for each of these phases. In addition, information on school characteristics and school policies will be obtained from school administrators, and information on neighborhood and community characteristics gathered from independent sources. Interviews with adolescents and their parents will be repeated after a one-year interval, providing a longitudinal component to the study.

The accuracy of data collected by the study will be assured by several special features. The study will apply new computer-based methods for data collection that greatly increase the privacy of the interview for study participants. Pilot work with similar methods suggests that they offer substantial improvement in the quality of information on sensitive behaviors and health outcomes compared with conventional survey procedures. The study also includes a number of built-in validity checks, including a small independent national area sample of adolescents to compare with the school-based sample.

Mr. Smith: Do you expect any reluctance to participate on the part of parents or schools?

Dr. Alexander: The data collection contractor for the study, the National Opinion Research Center at the University of Chicago, has a superb record for the successful recruitment of schools in studies conducted by the Department of Education, as well as in obtaining parental cooperation for studies of adolescents. Of course, participation in the study is completely voluntary, and the study will be completely explained to school administrators, adolescents, and their parents before informed consent is obtained. We expect that school nonparticipation can be kept to a minimum by providing full information about the study including the fact that the Congress mandated that it be done, and the noncontroversial nature of the in-school data collection.

Mr. Smith: What are the major subject areas of the survey, and what information already exists in the field?

Dr. Alexander: The study addresses a comprehensive range of adolescent health outcomes, including physical health status (height and weight, injuries, physical disabilities, mental health, sleep disorders, days lost from school through illness), health behaviors (eating disorders, substance use and abuse, intentional and unintentional injury, sexual behavior, prevention of pregnancy and sexually transmitted diseases including AIDS, nutrition, exercise and fitness), and health insurance and use of health services. This is the first national comprehensive study of the determinants of adolescent health. It moves beyond information from existing studies by virtue of its focus on all aspects of adolescent health, its goal of understanding the determinants of health rather than monitoring behavioral trends, and by its attention to the influences on health in the adolescent's social and physical environment.

Mr. Smith: What is the annual and lifetime cost of the survey?

Dr. Alexander: The survey will cost $4.1 million in FY 1994, and $8.1 million in FY 1995. To date, $2.0 million has been committed by the NICHD to the project in FY 1994, and $4.0 million is included in the NICHD FY 1995 Request. Co-funding by other NIH offices and institutes is actively being sought in an attempt to make up the difference. The total cost of the survey, over a five-year project period, is $21.5 million.

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

Mr. Smith: Has the National Center for Medical Rehabilitation Research reached its full operating level with the FY 1994 Appropriation?

Dr. Alexander. The National Center for Medical Rehabilitation Research (NCMRR) budget for FY 1994 is $14.0 million, an increase of 40 percent over the FY 1993 level. The center, however, has not yet reached its full operating level. The research plan developed by the National Advisory Board on Medical Rehabilitation Research specifies seven emphasis areas. Reflecting the need to prioritize within the Institute's total budget, NCMRR is providing less than operating level support for research in five of those areas--assistive technology, improving functional mobility, facilitating behavioral adaptation to functional loss, improving the scientific measurement of disabilities, and evaluating the effectiveness of medical rehabilitation practices. Additionally, the Center has not had funds to support interdisciplinary research centers, proposed by our Advisory Board, which are so appropriate for a field like medical rehabilitation.

Mr. Smith: What research areas is the Center targeting? Has it expanded its scope beyond the three initial research areas that were identified?

Dr. Alexander: The preponderance of the Center's funding commitments are in only two of the seven emphasis areas designated in the research plan. Those areas are: a) research training and b) organ dysfunction (e.g., of the bladder) among persons with physical disabilities. Specifically, a number of projects are being funded concerned with bowel and bladder problems of persons with disabilities and with the sexuality and fertility issues experienced by these persons. Topics awaiting research initiatives include preventing secondary medical conditions specific to women with disabilities, promoting physical fitness among persons with disabilities, improving rehabilitation practices for children with disabling conditions including AIDS, dealing with the chronic pain associated with some disabling conditions, and assessing outcomes of medical rehabilitation practices.

Mr. Smith: Are the Center's grantees different from traditional NIH grantees because of the emphasis on assistive technology?

Dr. Alexander: One of the Center's goals has been to fund meritorious grant applications by researchers who have never received support by NIH. Indicative of success in that regard, the majority of current NCMRR grantees have not had NIH grants before.

Mr. Smith: Is the Center continuing to support institutional training grants to expand the field of rehabilitation researchers?

Dr. Alexander: In 1991, NCMRR's first operational year, seven institutional training (T-32) grants were funded. Six additional grants were funded in FY 1992, three more in FY 1993, and four during this fiscal year for a total of twenty awards. Though additional applications have not been solicited by means of a request for applications, Center staff members continue to receive inquiries from scientists wishing to apply for a T-32 award or for other forms of support for research training.

CONTRACEPTIVE TESTING NETWORK

Mr. Smith: What is your new Contraceptive Testing Network? Will the network be made up of your current contraceptive research centers?

Dr. Alexander: The Contraceptive Testing Network is to be a clinical network for conducting clinical trials necessary for FDA approval of new contraceptive drugs and devices and further evaluation of existing drugs and devices. The clinical trials units participating in this network will evaluate: (a) the pharmacokinetics, safety, and tolerance for oral, injected, implantable, or topical drugs as contraceptives; and (b) contraceptive efficacy and safety of contraceptive devices. The network will not be made of our current contraceptive research centers since their mandate is the development of new products.

Mr. Smith: Will there be a services component to the Network?

Dr. Alexander: A statistical and clinical coordinating center will support the network. However, this is a clinical research contraceptive testing network and not a center for dispensing of contraceptives or advice to contraceptive users.

MALE INFERTILITY

Mr. Smith: Describe for us how you are expanding your research in the area of male infertility. Are you playing catchup in this area compared to female infertility?

Dr. Alexander: The NICHD is continuing its sponsorship of a wide ranging base of general, investigator-initiated investigations as well as expanding this base with new exploratory initiatives on male infertility research. In order to identify high priority emphasis areas for expansion, the NICHD planned concept development workshops and conferences in 1993 and 1994. From the most recent NICHD conference in this area, a Request for Applications (RFA) entitled "Idiopathic Male Infertility" was announced on February 25, 1994. Research projects submitted for this initiative will be eligible for funding in December 1994.

The NICHD has also collaborated with other NIH Institutes in order to expand its research base in the area of male infertility. The NICHD will co-fund projects with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) studying the consequences of genitourinary viral infection on the testes, seminal vesicles, and epididymides. Projects from this initiative will be eligible for funding in September 1994. The NICHD has also cosponsored a coordinated program announcement with three other NIH Institutes (NIAID, NIDDK, NIA) soliciting research project applications focusing on the mucosal immunity system in the male and female genitourinary tract. The NICHD interest is on the immunobiology and immunopathology mechanisms associated with potential immunologic infertility.

In addition, the NICHD has expanded clinical trial topic areas in an RFA initiative announced on March 25, 1994 for the recompetition of the Cooperative Multicenter Reproductive Medicine Network. This RFA specifically solicits applications addressing the effects of varicocele on male fertility or the diagnosis and treatment of male infertility.

In order to plan a longer term, multi-year research agenda for supporting male infertility research emphasis areas, a conference entitled " Male Infertility and Impotence: Current Perspectives and New Directions for Basic and Clinical Research" is scheduled to be held August 2-4, 1994. The conference organizing committee, consisting of members nominated by the American Urological Association, the American Andrology Society, the NICHD and the NIDDK, has focused this conference on areas emphasizing research on the diagnosis, treatment, medical management or alleviation or cure of male infertility.

The present NICHD reproductive medicine research program reflects periodic and progressive updating of the Institute's research goals. New initiatives enable the Institute to facilitate the development of new research directions and investigator initiated research projects reflect, in general, the professionally chosen interests and activities of our extramural colleagues determined by the current state of knowledge and limitations in the field. In the case of infertility research, infertility is generally attributable to a male factor in about 40% of the couples experiencing infertility. NICHD funding for male infertility research is about 36% of the funding the NICHD allocated to infertility research. The NICHD infertility programs strive to maintain appropriate balances in the broad research base and to use targeted initiatives, where appropriate and justified, to either focus efforts on opening new research directions or to address identified gaps in our knowledge. The present activities of the NICHD in the field of male infertility research reflect the Institute's efforts to maintain this balance.

RETT SYNDROME

Mr. Smith: We understand that Rett syndrome is the subject of research in just a few places in the U.S. Is your Institute having any success in expanding the range of scientists interested in pursuing this field?

Dr. Alexander: The NICHD has been active in efforts to increase the number of investigators in studies on Rett Syndrome. The Institute supports the annual Rett Syndrome meetings, where clinicians, basic researchers, and health care providers interact. A recent program announcement from the Institute, "Genetic Disorders Causing Mental Retardation," highlighted Rett Syndrome, and program staff continues to encourage investigators to develop applications in this field. We are having some success in these efforts. Two new grant applications have been received for potential funding in FY 1994, and at least three others are in preparation.

FUNDING FOR RESEARCH AREAS

Mr. Smith: Provide estimated 1993-1995 spending on the following: pediatric AIDS (with a subtotal for clinical trials), sudden infant death syndrome, mental retardation, Rett syndrome, contraception, infertility, and fibroids/endometriosis/pelvic inflammatory disease.

Dr. Alexander: The support levels for these research areas are as follows.

(Dollars in thousands)

	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
Pediatric AIDS........	$33,649	$48,900	$52,100
(clinical Trials)....	(16,397)	(24,000)	(25,200)
Sudden Infant Death Syndrome			
Total...............	41,952	43,000	44,500
Primary.............	9,918	10,300	10,700
Mental Retardation....	53,021	54,700	56,700
Rett Syndrome.........	1,526	1,600	1,650
Contraception.........	23,098	27,700	35,400
Infertility...........	9,135	9,300	9,600
Fibroids/endometriosis/ pelvic inflammatory disease............	2,350	2,500	2,600

NATIONAL CENTER FOR MEDICAL REHABILITATION RESEARCH

Mr. Smith: Provide a 1993-1995 mechanism table for funding for the National Center for Medical Rehabilitation Research, including intramural and RMS.

Dr. Alexander: The support levels for the National Center for Medical Rehabilitation Research by funding mechanism are as follows.

(Dollars in thousands)

	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
Research Project Grants..	$7,807	$11,186	$11,500
Research Centers.........	---	---	---
Other Research Grants....	45	50	50
Research Training........	1,521	2,239	2,302
R&D Contracts............	460	275	1,000
Total Extramural......	9,995	14,000	15,112
Intramural Research......	54	500	500
RMS......................	1,296	1,500	1,557
Total.................	11,318	16,000	17,169

SIDS RESEARCH

Mr. Smith: Have you developed a follow-on five year plan for SIDS research? Is there a funding level associated with the plan's recommendations?

Dr. Alexander: FY 1994 is the 5th year of the first five year plan. NICHD is currently developing a second 5-year plan which will be submitted to the Appropriations Committee this fall. Since the development of the Plan is still underway, there is currently no specific funding level that associated with the Plan's recommendation. Preliminary estimates indicate, however, that approximately $17.0 million would be required to fully meet the plans first year objectives.

Mr. Smith: Identify the number, type and subject matter of all research centers supported in 1994.

Dr. Alexander: The information follows:

Number	Type	Subject Matter
15	Specialized Comprehensive	Mental Retardation
3	Specialized Comprehensive	Learning Disabilities
9	Specialized Comprehensive	Perinatal Research
19	Specialized Comprehensive	Child Health Research
16	Specialized Comprehensive	Reproductive Sciences
3	Specialized Comprehensive	Contraceptive Research
2	Specialized Comprehensive	Infertility Research
10	Specialized Comprehensive	Demographic and Behavioral Sciences
77	Total	

GENE THERAPY

Mr. Smith: We know that human tissue and organs and human biomaterials have become very important for many area of disease research such as Diabetes, Cancer, and gene therapy. Have you moved to enlarge and continue support for the National Disease Research Interchange (NDRI), the national program collecting and distributing human tissue and organs for research?

Dr. Alexander: One of the missions of the National Center for Research Resources (NCRR) of the NIH is to support resources which provide critical biological materials such as cell lines, microorganisms, DNA probes, human tissues and organs, and lower organisms to the biomedical research community. Based on information provided by the NCRR, one such facility, the National Disease Research Interchange (NDRI) has been supported with a cooperative agreement by NCRR since FY 1989. Currently, NCRR is continuing its support of the NDRI through an administrative supplement until July 1994 while the current NDRI competitive application is undergoing review. After the National Advisory Research Resources Council meeting in June, a recommendation will be made as to the appropriateness and level of funding of the NDRI.

INFANT MORTALITY

Mr. Stokes: What opportunities in infant mortality are at hand and built into the FY 1995 request?

Dr. Alexander. The FY 1995 budget request takes advantage of opportunities in the infant mortality field including:

- the initiation of the first year of a new Sudden Infant Death Syndrome (SIDS) Research Five-Year Plan;
- the launching of on-site operations of the new intramural Perinatal Research Branch located in the District of Columbia to focus on clinical and basic research on high-risk pregnancy and infancy especially in minority populations;
- the continued development of a network of Pediatric Pharmacology Research Units to study drug action and disposition in infants and children and provide clinical data on drugs necessary for FDA approval for childhood use;
- the continued implementation of District of Columbia Infant Mortality Collaborative Research Initiative to devise and evaluate community interventions to reduce infant morbidity and mortality among disadvantaged, largely minority populations;
- and the extension of clinical trials in the Institute's Maternal-Fetal Medicine Unit (MFMU) Network and Neonatal Intensive Care Unit (NICU) Network. These include studies on the prevention of preeclampsia, premature rupture of the membranes, and preterm labor, as well as the prevention of bronchopulmonary dysplasia, and neonatal intracranial hemorrhage, research on the neurodevelopmental outcome of infants exposed *in utero* to cocaine in collaboration with NIDA, and, in collaboration with NHLBI, the establishment of a registry and clinical trial on asthma in pregnancy.

Mr. Stokes: What are the opportunities that are now ready to be exploited but are not included in the Budget Request, and what is the estimated cost?

Dr. Alexander: While much is being done in the area of infant mortality there are still many research opportunities ready to be exploited that are not included in the FY 1995 budget request. In order to pursue all of these opportunities an additional $35 million is required. These opportunities include:

- additional clinical trials funded through the NICU network in such areas as:
    - the prevention/treatment of brain damage associated with severe asphyxia,
    - methods to achieve a transfusion-free intensive care unit;
    - new nutritional strategies for VLBW infants,
    - prevention of necrotizing enterocolitis,
    - new methods to diagnose and prevent infections in VLBW infants,

  - the influence of environment on neurologic development, and
  - expansion of the current trial of inhaled nitric oxide for the treatment of pulmonary hypertension;

- additional clinical trials funded through the MFMU network in such areas as:

  - antenatal steroids in premature rupture of membranes and prolonged threatened delivery,
  - techniques to increase the administration of antenatal steroids,
  - use of new methods of preventing preterm delivery including new tocolytics,
  - treatment of specific reproductive tract infections to reduce the risk of preterm birth;

- Expansion of the D.C. Perinatalogy Research Branch; and

- Expansion of the NICHD SIDS program,

- Support for additional basic science in the areas of prevention of preterm delivery and the major sequelae of prematurity, assessment of fetal well being, and application of the techniques of molecular biology to fetal development.

NORMATIVE BEHAVIOR

Mr. Stokes: As you know, I have been very interested in and appreciate NICHD's long-term commitment to the initiative on normative development of ethnic minorities. The scientific study of the normative development and conditions that influence it are imperative to furthering advances in this area. Can you tell us what the status is of the Normative Behavior Research Initiative, and tell us about the progress that has been made? How much is included in the FY 1995 Budget Request for this initiative? How does this amount compare with FY 1994?

Dr. Alexander: The five grants awarded, in April 1993 by NICHD, in connection with the RFA on Normative Development of Ethnic Minorities have been under way for just one year. Each of the applicants have begun to operationalize their planned studies, but preliminary findings are not yet available since substantive data collection will begin during this fiscal year.

In FY 1994, the Institute also plans to fund new grants in connection with an RFA entitled Behavioral Development in Middle Childhood. The Institute anticipates that several of the awarded grants will focus upon studies that will involve normative development of minority children during middle childhood.

The FY 1995 budget request includes approximately $1.9 million for these two initiatives. This compares to $1.8 million in FY 1994.

In addition to the grants mentioned above, there is a cooperative agreement to investigate the effects of day care on normative development. The study includes sites that are following, in aggregate, the normative development of some 1,200 children from birth to age three to gain an understanding of their social, emotional, and intellectual development. Minority children range between five to thirty percent across the ten sites. Excellent progress has been made. Data have been collected on all of the variables described above for all of the children through the age of two years.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly. How much is included in the FY 1995 Budget Request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Alexander: Significant progress has been made in several areas of research that are relevant to gene therapy. The number of cloned genes is rapidly increasing, and we now have a better understanding of the nature of the disease-producing mutations. We also know much more about the regulation of gene expression and have available improved vehicles to deliver the genes to target organs. Molecular techniques are also now available to produce animal models for genetic disorders. Results from experiments on these animal models will be obtained before we can embark on clinical trials on human genetic disorders. Within the NICHD, the diseases and disorders that offer most hope through further advances and investments in gene therapy include:

- defects of amino acid metabolism (phenylketonuria);
- urea cycle defects (OTC or ornithine transcarbamylase deficiency);
- organic acidemia (methylmalonic acidemia);
- carbohydrate metabolism (galactosemia);
- peroxisomal disorders (adrenoleukodystrophy);
- trace metal deficiency (Menkes disease);
- lysosomal storage disease (Gaucher disease);
- disorders of purine metabolism (Lesch-Nyhan syndrome);
- glycogen storage diseases;
- disorders of bilirubin metabolism; and
- heritable forms of emphysema.

Target organs for these conditions include the liver, bone marrow, central nervous system, and the respiratory system.

In November 1993, the NICHD issued an RFA to develop new technologies, or improve existing ones, for gene therapy targeted towards disorders causing mental retardation. Three to five awards are expected to be made in response to this RFA in early FY 1995.

The FY 1995 NICHD Budget Request includes $5,000,000 for research on gene therapy. The estimate for FY 1994 is $1,900,000. Actual obligations in FY 1993 were $1,864,000.

MINORITY HEALTH

Mr. Stokes: As the Director of an Institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues -- while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and -- while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Alexander: As the Director of the NICHD, I am troubled and concerned by the correct statement that the minority health crisis continues. Despite the fact that we have made steady progress--for instance, infant mortality among African-Americans has dropped from nearly 23 infant deaths per 1,000 live births to less than 18 in the last decade, the rate of infant mortality continues to be more than twice as high for blacks as for whites. What is so troubling is that as we continue to make improvements in the health of all Americans, we have not been able to significantly reduce the disparity between the incidence of disease and disorder among minorities and non-minorities. Our Institute has placed increasing emphasis on the need to directly attack and reduce this disparity.

In addition to continuing and expanding efforts to increase our knowledge of how to prevent the diseases and disorders that keep the infant mortality rate high, particularly among minorities, we are seeking to improve education activities to apply the knowledge we have. Two examples of our public and professional education efforts include increasing the use of corticosteroids to treat premature infants--a proven means of preventing premature infant death, and the national "back to sleep" public education campaign to get parents to put their infants to sleep on their backs or sides rather than their on their stomachs as a means of reducing the incidence of SIDS--the leading cause of infant death after the first month of life.

RESEARCH PIPELINE

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Alexander: Of the biomedical and behavioral research fields that relate to the mission of the NICHD, there are those that have expressed a concern that the supply of technologically up-to-date new investigators "in the pipeline" is either decreasing or failing to increase at a fast enough rate. Indeed, the number of trainees supported by the NICHD has been decreasing for over a decade. It is generally believed that the Institute's continuing low funding success rate has as much impact on the "pipeline" as the level of direct support for trainees.

RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Alexander: Two examples of the most recent exciting and promising clinical opportunities with research investment benefits are fetoscopic surgery and anti-HIV therapies. Using a noninvasive technology called color doppler ultrasonography, NICHD intramural scientists were able to tie off, *in utero*, the umbilical cord of a malformed twin lacking a heart and save the life of the other twin whose heart was pumping strenuously for both fetuses. With continued support for research in this area, operative fetoscopy may be used to treat and evaluate many previously untreatable fetal abnormalities and reduce infant morbidity and mortality.

Some of the anti-HIV drug trials recently demonstrated promising results. NICHD in part, sponsored the AIDS Clinical Trials Group Study 076 in which pregnant women received either AZT or a placebo during pregnancy and labor, while their infants received the same treatment, either AZT or placebo, within 24 hours after birth and for six weeks thereafter. When a preliminary analysis demonstrated that AZT reduced HIV transmission from mother to infant by two-thirds, when both received therapy, the investigators stopped the control group early and offered the treatment to all the pregnant women. Another trial demonstrated that intravenous immunoglobulin reduced the number of bacterial infections in HIV-infected children. Further investment in this research may lead to more ways of preventing HIV infection in infants and children.

A third example of promising clinical research opportunities is the NICHD testing of a new acellular pertussis vaccine which was developed in our intramural laboratories. This vaccine is currently being tested in Sweden for efficacy and the U.S. for safety and immunogenicity. So far, the adverse side effects of this vaccine have been negligible. Assuming the preliminary observations are confirmed, the manufacturer of this vaccine plans to seek a license from the FDA to market the product in the U.S. by late 1994 or early 1995.

MINORITY HEALTH

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Alexander: In general, all research funding decisions made by the NICHD consider the pressing public health needs, especially the incidence and prevalence of the diseases and disorders upon which the research is likely to impact. An example of how this is expressed is the Institute's requirement that proposed research activities must be evaluated in light of the relevant goals in the Healthy People 2000 health plan for the Nation. With our concern for the disparity with which many health conditions affect minorities, there is special emphasis placed on conducting and supporting research that addresses the health needs of minorities. That priority is expressed in the planning, peer review, and implementation of NICHD activities. Indeed, because minorities are so frequently disproportionately affected, our efforts to meet the health needs of the American people regularly place special emphasis on those conditions that have the greatest impact on minorities.

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your Institute?

Dr. Alexander: Over the past year the NICHD expanded its initiatives in minority health research and research training through RFAs. For example, it was through an RFA that the Cooperative Community-Based Perinatal Research Program was launched. This initiative will develop and test a variety of interventions for reducing high infant mortality among predominantly minority populations in Washington D.C.

Another RFA entitled "Ethnic Minority Families With Retarded Members", is designed to stimulate research on the unique qualities of ethnic minority families with mentally retarded or developmentally disabled members. This research is intended to explore traditional beliefs and values, and responses to these special disabled individuals within minority groups. In addition the researchers will study formal and informal support systems and the impact of ethnicity on the use of various support service agencies.

Recently, a RFA entitled, "Hispanic Child Health: Social, Behavioral and Cultural Factors," was issued to address 1) factors that promote low rates of infant mortality and chronic disease in some Hispanic subgroups, 2) how migration, its antecedents and consequences affect the health of Hispanic subgroups and their children; 3) how trends in fertility and mortality may change over time and space in response to changing characteristics of the population; and 4) which factors have led to different health outcomes among different Hispanic subpopulations, and whether social, demographic, behavioral, and biological differences can predict health outcomes.

The NICHD also provides support for a grant entitled "Short-Term Training Students in Health Professional Schools." This grant supports medical students to carry out pediatrics-related research at a medical school other than their own. In 1994, the

Institute funded a $20,000 administrative supplement earmarked for the support of minority students under this program.

In the peer review of Institutional National Research Service Award applications, the NICHD places special emphasis on the evaluation of applicants' plans and accomplishments regarding the recruitment of minorities into their training programs. All competing applications for institutional training grants must include a detailed plan for minority recruitment. Furthermore, all renewal (competing continuation) applications must also include a report on the training program's recruitment and retention record during the previous award period. Institute peer review committees are given extensive orientation on NIH and NICHD policy regarding minority research training, with emphasis on the need to critically examine and evaluate all plans for recruitment and records of recruitment and retention of minority trainees. If the minority recruitment activities of a training program are judged to be unacceptable by the review committee, the Institute withholds funding until an acceptable plan is submitted.

The NICHD is also initiating a program designed to heighten awareness among the scientific community of the importance of actively involving minority participants in conferences and workshops supported with NICHD funds. Before it is possible to use the adequacy of minority participation as a criterion for funding, it is necessary to educate the scientific community that this is an issue that is viewed as extremely important by the Institute and an issue that must be considered by them in the preparation of their requests for funding. For all applications for conference/workshop funding, Institute review committees are instructed to evaluate the adequacy of minority participation in the organization and planning of the conference, and the adequacy of the plans to actively recruit minority presenters and attendees at the event. A section of the written review is devoted to the reviewers' comments in this regard. Initially, this section will help to inform the scientific community of the importance of actively promoting the participation of minority scientists. In the future, it is anticipated that the evaluation of plans for minority involvement will enter into the Institute's funding considerations.

Mr. Stokes: How does your Institute identify its priorities for investments in minority research and research training?

Dr. Alexander: With the broad mission to "improve the health of the Nation" in the areas of research that relate to child health and human development, the NICHD establishes its priorities on the basis of those research opportunities most likely to contribute to the betterment of the health of the American people. In research activities focused on minorities, as well as non-minorities, priority is placed on the potential impact on the greatest health needs, the science that appears to offer the most promise of achieving its objectives, and the research which we have adequate resources to address. Even in its support for basic research, emphasis is placed on the best science, that is, the research that holds the most promise for developing new knowledge that is likely to advance our understanding and, therefore, lead to improvements in public health. Decisions on more applied research are considered in terms of their support for the goals in the Healthy People 2000 health plan for the Nation, specifically, its potential impact on the incidence and prevalence of the health conditions being studied. With the disparity with which so many health problems affect minorities, it is likely that decisions based on incidence and prevalence will place some priority on those conditions most common among minorities.

Mr. Stokes: When the Office of Research on Minority Health provides funds to your Institute, do these funds typically augment existing minority programs or efforts, or do they replace funds your Institute previously invested in its minority research and research training initiatives, elaborate.

Dr. Alexander: The Institute collaborates closely with the NIH Office of Research on Minority Health (ORMH), with the Minority Health Initiative (MHI) as the principal focus. NICHD, with support from the ORMH, conducts projects in several areas of the MHI, including infant mortality, youth behavior, and an intramural project investigating hemochromatosis. All of these studies are new efforts of the Institute. Funds from ORMH have been used only to augment NICHD minority programs; support from ORMH does not replace Institute funds.

Mr. Stokes: When your Institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health? To what extent is there a collaborative relationship between the two organizations, elaborate.

Dr. Alexander: Yes, the NICHD does consult and work closely with the NIH Office of Research on Minority Health (ORMH) when it is developing new minority initiatives. Frequently, our staff will work with ORMH staff in the planning of NICHD projects with significant focus on minority groups. Similarly, our staff offers guidance and support for ORMH projects in areas of our expertise. At the present time, the NICHD and ORMH are working together and co-funding a major infant mortality initiative; a minority youth behavior initiative; a minority supplement for a Native American researcher; a major intramural study of hemochromatosis in African Americans; and six other wide-ranging minority research projects.

CLINICAL TRIALS

Mr. Stokes: How much is included in the FY 1995 Budget Request for clinical trials? How does this amount compare with the amount invested in clinical trials in FY 1994, and FY 1993? Would you please comment on the economic benefits, and the quality of life benefits of some of the major clinical trials supported by your Institute?

Dr. Alexander: The NICHD FY 1995 Budget Request contains $54,600,000 for clinical trials ($79,800,000 with AIDS clinical trials included). The amount for FY 1994 is $48,800,000 ($72,800,000 including AIDS), and for FY 1993 it was $47,054,000 ($63,451,000 including AIDS).

Clinical research supported by the NICHD that is likely to yield economic benefits includes the use of corticosteroids during preterm labor, the use of tinmesoporphyrin in preterm jaundiced infants, and the efficacy of routine ultrasound during prenatal care. Corticosteroids used in women who are threatening to deliver between 24 and 34 weeks of pregnancy can prevent Respiratory Distress syndrome by hastening lung maturation, and significantly reduce the incidence of intraventricular hemorrhage. At less than $10 per administered dose, conservative estimates show that even if corticosteroids are used in only 60% of premature births, the nation could save $157 million in hospital costs alone.

Each year in the U.S., about 250,000 U.S. infants develop jaundice severe enough to warrant treatment. In a study of 517 preterm infants receiving a single small dose of a new drug, tinmesoporphyrin (SnMP), peak bilirubin levels were reduced by 41 percent and diminished the necessity of standard treatment, known as phototherapy, which requires long and intense exposure to special lights in the hospital prohibiting infant-family interaction. Thus cost savings are likely.

A clinical trial to study the efficacy of routine ultrasound screening of all pregnancies to improve perinatal outcomes showed that the routine use of two screening sonograms failed to reduce perinatal morbidity or mortality in low-risk pregnancies when compared to the selective use of ultrasound based on clinical judgement. Preliminary data analysis determined that the average cost of an ultrasound is between $185 and $350. With an average of 4 million U.S. pregnancies per year, 80 percent of which are low-risk, early indications are that selective use of ultrasound could produce significant cost savings.

Mr. Stokes: To what extent has the Institute increased the number of minorities participating in its clinical trials, what progress is being made?

Dr. Alexander: Although much of NICHD-supported research has important implications for all cultural and ethnic populations, some of the research specifically targets minorities based on the health problems that disproportionately affect minorities. NICHD clinical studies with predominantly enrolled minority populations include problems of Sudden Infant Death Syndrome, low birth weight, preterm delivery, maternal-infant transmission of HIV, teenage pregnancy, adolescent risk-taking behavior associated with STDs and HIV infections, adolescent obesity, and genetic or psychosocial-cultural influences that diminish quality of life and health among minority families and children.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Alexander: The NICHD has made minority supplement awards starting in FY 1989. In FY 1993, the Institute made 58 minority supplement awards for a total of $1.8 million. Since most of the recipients are at the pre-doctoral level (some are high-schoolers), it is still too early to see results of successful investigator applicants. NIH, however, has in place a system to evaluate the success of this program, and which will soon be able to provide the information that you have requested.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes: What are some to the major initiatives underway at your Institute to increase the participation of historically black colleges and universities in biomedical research?

Dr. Alexander: A look at the NICHD 1994 Historically Black Colleges and Universities (HBCU) Plan developed in 1992, indicates a goal to increase levels of HBCU funding support by 30 percent. Our evaluation reveals that the Institute has met that goal set for 1994. The NICHD currently has eight HBCU projects underway involving research in reproductive basic science areas that are critical for sexual development, AIDS prevention models for minority women, and community-based interventions to reduce infant mortality.

MINORITY EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Institute? How many employees in your Institute are in GS-15 and above positions? In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Alexander: There are currently 55 positions in the Institute, GS-15 or above. There are 54 employees in these positions (1 is vacant). One African-American is at the GS-15 level. She is a "Research Microbiologist." We have no pending exception requests for appointments at the GS-15 level and above. The NIH requested relief from the Public Health Service hiring freeze imposed in December 1993 because NIH had successfully managed its FTE ceiling. The request is under consideration by the PHS. If the freeze was lifted, we would be able to recruit from a larger population of candidates, thereby increasing the potential to appoint minority applicants.

PREVENTION RESEARCH

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Alexander: Major health promotion and disease prevention initiatives of the NICHD include: the development of female-controlled barrier contraceptives to prevent the spread of sexually-transmitted diseases, including HIV, as well as prevent pregnancy; a comprehensive, longitudinal national study of adolescent health to inform interventions to improve adolescent health; research to improve and increase the use of prenatal care; studies to prevent birth defects; research to develop the means of preventing childhood injuries; the development of behavioral approaches to increasing childhood immunization rates; studies to predict and prevent insulin-dependent diabetes mellitus (type I or juvenile diabetes); development of the means to eliminate the maternal-fetal transmission of HIV infection; the prevention of adolescent pregnancy; testing and licensing new NICHD-developed vaccines for childhood diseases, diarrheal diseases, and tuberculosis; preventing the complications of pregnancy; improving contraceptive availability and use; the prevention of unnecessary hysterectomy; and the prevention of bowel and bladder management problems and decubitus ulcers (bed sores) in persons with disabilities.

These biomedical and behavioral research activities, which focus on preventing unintended pregnancies, improving birth outcomes, preventing infant and childhood morbidity and mortality, and enhancing the functioning of persons with disabilities are important to the Nation's public health and economic interest, as well as for health care reform, and cover a full range of basic, applied, and clinical research.

BIOTECHNOLOGY

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Alexander: Among the important research areas supported by NICHD are fertility, infertility, and basic development from early embryogenesis to maturity. Biotechnology advances have been and will continue to be critical in understanding the basic mechanisms involved in reproductive processes and early normal and abnormal development.

In some basic research supported by NICHD, recombinant DNA technology is being used to address the mechanisms underlying the development of sperm and eggs and their interaction during fertilization.

Gene mapping is used to understand the causes of developmental defects and mental retardation in other research. Some disorders of particular interest are Down syndrome, phenylketonuria (PKU), Fragile-X, and X-linked adrenoleukodystrophy.

In addition, the Institute is promoting research on gene therapy for inborn errors of metabolism and other inherited developmental disorders as an alternative to traditional therapeutic approaches. Technologic advances of DNA-mediated gene transfer, microinjection and retroviral vectors are being used in animal models to develop safe and effective gene therapies for urea cycle disorders, Lesch-Nyhan syndrome, severe combined immunodeficiency disease and PKU.

As a support activity, NICHD would like to continue to provide investigators with biotechnology resources to support research. The Institute would like to continue to support its repository of human and mouse DNA probes and chromosome-specific libraries, the monoclonal antibody bank and the hybridoma collection.

Finally, the Institute would like to continue to develop the research foundation needed to continue progress in the field of medical rehabilitation. This requires the development of new materials and designs for producing improved state-of-the-art orthotics and prosthetics to restore functions to those with disabilities.

SUPPORT TO MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Alexander: The level of NICHD support provided to minority institutions in FY 1994 is $800,000. FY 1993 actual obligations were $764,000.

Mr. Stokes: Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Institute's programs and activities.

Dr. Alexander: The NICHD recently initiated funding support to assist Tuskegee University with strengthening and augmenting their human and physical resources for the conduct of biomedical research. This is a specific G12 award to help shape the infrastructure of research centers at predominately minority institutions offering doctorate degrees in the health professions or health-related sciences.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Alexander: The NICHD's proposed funding reflects support for programs designed to increase and encourage minority individuals to pursue biomedical research careers. These programs include administrative research supplements for underrepresented minority individuals and support for research training grants funding minority participation. An example of this type of activity is that this year, the NICHD funded a $20,000 administrative supplement earmarked for the support of minority students under a training grant entitled "Short-term Training Students in Health Professional Schools" This grant supports medical students to carry out pediatrics-related research at a medical school other than their own.

PERINATAL CARE

Mr. Stokes: The Health Resources and Services Administration indicated in its budget justification that their request includes funding to implement a case management approach to perinatal care in an effort to reduce infant mortality

As we examine the needs for perinatal care in an effort to reduce infant mortality, can you tell us what major accomplishments have been made in perinatal care? To what extent have they translated into application? What more needs to be done? In your professional judgement, will the proposed FY 1995 budget allow these needs to be explored and implemented? If not, in your professional judgement, what is the estimated cost to implement each?

Dr. Alexander: Recent advances in perinatal care have included the use of pulmonary surfactant to prevent respiratory distress in newborns, and recommended approaches to reduce the incidence of Group B Streptococcal disease in infants.

Clinical research supported by NICHD has provided some insight into other causes of perinatal morbidity and mortality, but at the same time has raised further questions that will need to be answered:

1. The Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) Clinical trial showed that prenatal ultrasound need not be done routinely in patients without medical indications for ultrasound. However, early detection of twins and growth retarded fetuses did not translate into improved perinatal outcomes for these subgroups. Thus, more research is needed to find more effective ways of managing such high risk pregnancies.

2. The Vaginal Infection and Prematurity (VIP) studies identified certain genital tract infections, such as bacterial vaginosis, that place a pregnancy at higher risk of premature delivery. Clinical trials are now indicated to determine if treating such infections during pregnancy will reduce the prematurity risk.

3. The recent NIH Consensus Conference on Antenatal Steroids strongly recommended the wider use of this medication to prevent neonatal morbidities. However, further research is needed to promote wider usage and to evaluate the impact of such a change.

4. Medications used to arrest preterm labor ("tocolytics") are thought to be only partially effective in delaying preterm birth. Many new tocolytic compounds have been synthesized, but extensive research is needed to evaluate their effectiveness and safety. A major, focused program of research and development in this area has not been pursued by the pharmaceutical industry. Thus, NIH support and leadership is urgently needed.

Of the foregoing needs, only the issue of prenatal infections can be addressed actively by the Maternal Fetal Medicine Units Network (MFMU) of the NICHD. An estimated $8 million per year would be required to develop significant approaches to the other needs.

RETT SYNDROME

Mr. Hoyer: As you know, Dr. Alexander, I've been interested in the progress you've been making with research on Rett Syndrome, a disorder that disproportionately affects girls. Please share with the Committee your recent research findings on Rett Syndrome and related disorders. What efforts have been taken by NICHD to stimulate research in this area?

Dr. Alexander: Recent neuropathological studies suggest that at some point right around birth - during the most dynamic stage of brain development - basal forebrain neurons fail to develop properly. This focuses attention on a window of vulnerability in the infant brain when certain developmental factors may be altered. These studies underscore the observation that Rett Syndrome is a neurodevelopmental rather than a neurodegenerative disease. Neurochemical and brain imaging studies reveal specific alterations in the neurotransmitters dopamine, acetylcholine, and glutamate, which would account for the movement disorders, cognitive deficits, and seizures. Because of its predominance in females, molecular genetic studies continue to focus on the X chromosome, although more complex genetic mechanisms are now being considered. Over the past few years, molecular genetic approaches have helped track down the basis of other neurological and developmental disorders. In addition, nutritional studies have shown that high protein/high energy diets are effective in managing the growth and metabolic problems associated with Rett. It should be noted that many of these studies would not be possible without the tremendous support of the Rett syndrome parent groups.

NICHD currently supports two large program projects: one at Baylor and another at Kennedy Krieger/Johns Hopkins. Both of these programs include collaborations with other researchers across the United States and abroad. NICHD continues to support the annual Rett Syndrome meetings, which provide an important forum for clinicians, basic researchers, and health care providers to interact. The next meeting is scheduled during October, 1994 in Portland, Oregon. As for efforts to stimulate additional research, Rett syndrome was highlighted in a recent program announcement from NICHD entitled Genetic Disorders Causing Mental Retardation. Program staff has encouraged specific Rett researchers and clinicians to develop applications to NIH. This has resulted in two new submissions for September 1994 Council, and at least three others in preparation, mostly focusing on neuropathology and genetics. Autistic-like behaviors are common in Rett girls, and NIH is developing broad initiatives in the area of Autism research.

ADD HEALTH

Mr. Hoyer: I understand NICHD is initiating a nationwide comprehensive study of the state of adolescent health. Can you tell the Committee about this study? What is your estimate of the total cost of this research, and how much is included for it in your FY 94 and 95 budgets?

Dr. Alexander: The ADD HEALTH study is the first national, comprehensive study of the determinants of adolescent health. This innovative study, funded in response to a Congressional directive, will investigate the impact of the adolescent's social and physical environment - the family, peer group, school, neighborhood and community - on health behaviors and health outcomes. Over 19,000 adolescents and their parents will participate. The study will be conducted by Dr. J. Richard Udry, Kenan Professor of Maternal and Child Health and of Sociology at the University of North Carolina at Chapel Hill. The investigators have developed a comprehensive plan for obtaining signed, informed consent from both parents and adolescents, and for protecting the confidentiality of all the data collected in this project.

The study will cost $21.5 million over five years, including $4.1 million in FY 1994 and $8.1 million in FY 1995. To date, $2 million has been committed by NICHD to the project in FY 1994 funds and $4 million is included in the NICHD Budget Request for FY 1995. Co-funding by other NIH offices and Institutes is actively being sought in an attempt to make up the difference.

DEMOGRAPHIC AND BEHAVIORAL SCIENCES RESEARCH CENTER

Mr. Hoyer: Last year the NICHD indicated that supporting the work of an additional demographic and behavioral sciences research center was a high priority for you. Since you weren't able to add such a new center this year, do you plan to do so in the coming fiscal year?

Dr. Alexander: The FY 1995 President's Request for the NICHD allows for one additional research center grant, and it is planned that it will be in the demographic and behavioral sciences program.

NICHD SUCCESS RATE

Mr. Hoyer: Dr. Alexander, what percentage of approved grants does NICHD expect to fund in FY 1995 under the Administration's Budget Request, and has that figure been changing in recent years? What are the policy implications of this (low) success rate? Has the Institute been compelled to negotiate further reductions in funding with its grantees or contractors? Have these negotiated reductions affected the Institute's work?

Dr. Alexander. The success rate is determined by dividing the number of applications funded by the number that is reviewed. In both FY 1994 and 1995, the NICHD expects to fund research project grants at a success rate of 21 percent. That percentage is about the same as it was in FY 1993 (21.3 percent), but lower than it was the previous two years (FY 1992, 26.3 percent, and FY 1991, 25.1 percent). The Institute does negotiate with both grantees and contractors to fund projects at lower amounts than originally recommended in order to enable other high quality projects to be funded. The impact of these further negotiated reductions is that projects are scaled back, and sometimes we do not see results as quickly as we would like. However, considering the wide scope of the Institute's mandate, and newly established programs, such as those in the National Center for Medical Rehabilitation Research.

SAVINGS GENERATED BY RESEARCH

Mrs. Lowey: Can you estimate the savings associated with the development of the drug that prevents the jaundice in infants?

Dr. Alexander: Ten percent (400,000) of full-term newborns and approximately 280,000 preterm newborns develop hyperbilirubinemia annually. A conservative estimate of the additional costs associated with the medical tests, treatment, and extended hospitalization for hyperbilirubinemia is $340 million per year ($500 per infant). A new drug whose estimated cost will be between $0.10 and $1.00 is under study. If it proves to be safe and effective, the health care savings will be significant.

ADOLESCENT HEALTH STUDY

Mrs. Lowey: I am pleased to see the Institute proceeding with the Adolescent Health Study. What can you tell us more about this important initiative?

Dr. Alexander: The ADD HEALTH study is the first national, comprehensive study of the determinants of adolescent health. This innovative study, funded in response to a Congressional directive, will investigate the impact of the adolescent's social and physical environment - the family, peer group, school, neighborhood and community - on health behaviors and health outcomes. Over 19,000 adolescents and their parents will participate. The study will be conducted by Dr. J. Richard Udry, Kenan Professor of Maternal and Child Health and of Sociology at the University of North Carolina at Chapel Hill. The investigators have developed a comprehensive plan for obtaining signed, informed consent from both parents and adolescents, and for protecting the confidentiality of all the data collected in this project.

CALCIUM SUPPLEMENTS AND BONE DENSITY

Mrs. Lowey: Can you update the Committee about the Institute's findings with regard to the impact of calcium supplements on the bone density of adolescent girls?

Dr. Alexander: Calcium plays a vital role in many biological functions including skeleton formation. The NICHD recently supported a randomized, double-blind, placebo-controlled clinical trial to determine the effects of oral calcium supplementation on bone density in adolescent girls. Results show that a daily supplement of 500 mg of calcium citrate malate increases the rate of acquisition of bone. The supplemented group compared with the placebo group gained 24 grams more of bone during the 24-month trial and had greater increases of lumbar spine bone density, lumbar spine bone mineral content, and total body bone mineral density. At this rate, the supplemented girls would have 6 percent greater bone density by age 18, which would provide protection against osteoporotic fractures later in life. These findings demonstrate that increasing daily calcium intake from 80% of the recommended daily allowance to 110% during adolescence can increase peak bone density and may prevent future osteoporosis and bone fractures.

ENDOMETRIOSIS RESEARCH

Mrs. Lowey: The budget request includes funds for 3 additional cooperative clinical units which will conduct research on gynecological disorders, such as endometriosis. This would be a 12.6 percent increase in this area. How specifically do you plan to use this increase?

Dr. Alexander: The 12.6 percent increase in NICHD Cooperative Clinical Research will result in a total of $23,561,000 in FY 1995, compared to $20,924,000 in FY 1994. As you mentioned, the key component of the increase will be the expansion of the Reproductive Medicine Network. Specifically, this expansion is expected to include clinical trials of new treatments for gynecologic disorders such as fibroids and endometriosis, as well as additional studies in the area of infertility, both male and female factor.

INFANT MORTALITY

Mrs. Lowey: What is the nation's current infant mortality rate and how does it compare with what the rate was 10 and 20 years ago? What are your priority activities designed to learn more about how we can make progress on this tragic problem?

Dr. Alexander: The latest provisional National Center for Health Statistics data show a total infant mortality rate in 1992 of 8.5 per 1,000 live births, five percent lower than the rate of 8.9 in 1991. The rate has decreased from 12.6 in 1980 and 20.0 in 1970. The largest contributor to the current infant mortality rate continues to be premature births, and more recently, extremely premature births occurring at less than 28 weeks of gestation. Black births have a higher proportion of these extremely premature births, and subsequent deaths, with infant mortality rates of 17.6 per 1,000 live births in 1991 compared to white rates of 7.3 per 1,000 live births. Leading causes of infant death after factors related to extreme prematurity are congenital anomalies, sudden infant death syndrome, and accidents.

NICHD continues to focus on prematurity through the Neonatal Intensive Care Unit Network which is conducting several studies to improve outcomes and decrease the costs of premature infants. Recent study results show antenatal corticosteroid therapy should result in a substantial decrease in neonatal morbidity and mortality. Several other large studies are directed to prevention of prematurity, sudden infant death syndrome and congenital malformations: (1) A major clinical trial evaluating calcium for preeclampsia prevention was started in 1991 with results expected in 1996. About one-fifth of infant deaths are associated with maternal preeclampsia which results in premature delivery; (2) NICHD is addressing sudden infant death syndrome through research grants to identify high risk infants and prevent SIDS deaths. Recently, prone sleeping position and inappropriate bedding have been identified as risk factors. A major effort has been started by NICHD to educate physicians and parents on these factors; (3) Congenital malformations are being addressed through studies of spina bifida and other related defects. Studies are focusing on how folic acid can prevent these defects; (4) The Maternal-Fetal Medicine Network recently completed a study of use of aspirin to prevent preeclampsia, and subsequent preterm delivery, in low risk patients. The conclusion was that the benefit is insufficient to justify aspirin use in low risk patients at this time.

Several new initiatives have begun to address racial and ethnic disparities in infant mortality. The District of Columbia Infant Mortality Initiative is a cooperative agreement between NICHD and six DC institutions to address multiple facets including prematurity, intrauterine growth retardation, barriers to prenatal care, a trial of effectiveness of enhanced comprehensive prenatal care, impact of neonatal intensive care units, impact of parenting education, scope and determinants of injuries, lack of immunizations, prevention of adolescent pregnancy, reproductive decision making, and impact of managed care on the provision of prenatal and interconceptional services. In addition, the extramural program is seeking grantees to address factors related to Hispanic child health including infant mortality. Social, cultural, and behavioral factors will be addressed in the research grants. NICHD is currently funding a trial of zinc supplementation in pregnancy for black women to reduce preterm births, growth retardation and perinatal infections.

FULL-TIME EQUIVALENT REDUCTIONS (PERSONNEL)

Mrs. Lowey: The budget justification indicates that FTE's for the Institute will have declined by 54 since FY 1993. What is the impact of this cut on your ability to carry out your mission? How are you seeking to adjust?

Dr. Alexander. The FY 1995 NICHD President's Request will support 508 FTEs, as compared to 562 FTEs supported in FY 1993. Institute staff has been able to continue important ongoing research efforts, as well as to provide a satisfactory level of scientific and administrative management of NICHD research, both intramural and extramural. This has been accomplished through a diligent process of administrative improvements and efficiencies wherever possible, as well as significant efforts to maximize the use of remaining staff. Notwithstanding, there have been some adverse consequences on the amount and quality of research and oversight as a result of these FTE reductions. We continually make adjustments in order to accomplish our many missions. The period of time that you have cited, 1993 through 1995, was one in which the Institute established two major new programs. In one case, new legislation resulted in the establishment of the National Center for Medical Rehabilitation Research within the NICHD. Similarly, at the urging of the Congress, the Institute established the new intramural research Perinatal Research Branch, to address the serious problem of high infant mortality in the District of Columbia. Increases in FTEs would be required, normally, in order for the Institute to properly implement these new activities. Not having those additional FTEs has presented an even greater challenge to NICHD management to maximize the effectiveness of available FTEs.

BREAST CANCER

Mrs. Lowey: Please describe the Institute's research effort in breast cancer.

Dr. Alexander: The National Institute of Child Health and Human Development (NICHD) is conducting a large, multicenter study to determine if use of Oral Contraceptives and/or Hormone Replacement Therapy are associated with the development of breast cancer. The study will recruit 10,000 women from 35 to 64 years of age, both with and without breast cancer.

Participants will be asked to fill out a detailed questionnaire about their lifestyle and health habits. The study will examine alcohol consumption, smoking, use of medicinal drugs, exercise, menstrual characteristics, infertility, racial background, family history of breast cancer, and number of pregnancies.

Tissue samples will also be collected from women in the study. Researchers will use a variety of methods to study tissue from women who have developed breast cancer as well as from those who have not. Genetic studies and studies of tumor tissue will be done on selected subgroups of the study population.

Participating institutions are: the Emory University School of Public Health in Atlanta, GA; the Fred Hutchinson Cancer Research Center in Seattle, WA; the University of Pennsylvania School of Medicine in Philadelphia; the University of Southern California School of Medicine in Los Angeles; the Michigan Cancer Foundation in Detroit; and the Centers for Disease Control and Prevention in Atlanta, GA. Funding for this study has been provided in part through a reimbursable agreement by the National Cancer Institute.

PERINATAL RESEARCH

Mrs. Lowey: Can you summarize the accomplishments of the Perinatal Research Branch under your Institute?

Dr. Alexander: During the time since the Perinatal Research Branch of the NICHD's Division of Intramural Research was first discussed by the Congress in its annual appropriations report, this new Branch has been formally established, and its first chief, Dr. Roberto Romero, recruited. Dr. Romero was formerly a professor at the Yale University School of Medicine and is widely considered to be one of the country's leading researchers in the new field of maternal-fetal medicine. Moreover, because the Congress intended that this new Branch be physically established in an appropriate host institution within the District of Columbia (where the incidence of infant mortality remains very high), a $58 million contract has been awarded by the Institute to Georgetown University. The Georgetown Medical Center will serve as the major site for the clinics, laboratories, and offices of the Perinatal Research Branch, and satellite facilities are being established at the Howard University Hospital and the D.C. General Hospital. The satellites will also be operated under this large contract, which mainly provides for support staff and for space. The actual research staff will be intramural employees of the NICHD, and the patients to be enrolled in NICHD clinical research protocols will be admitted to the various D.C. hospital facilities covered under the contract. Even though the Branch will not be fully operational in Washington until this coming summer, research is already under way under Dr. Romero's direction. Two very important and recent accomplishments both relate to low birth weight, the main cause of infant mortality. In the first advance, Romero and his colleagues have developed more rapid and powerful methods for diagnosing endometritis, a bacterial infection of the uterus which is a leading cause of premature labor. Secondly, these researchers have pioneered the development of operative fetoscopy, an extraordinarily powerful technique in which fetal birth defects can be surgically repaired, using microscopic instruments, early in the development of the fetus without disrupting the pregnancy.

Mrs. Lowey: Is the FY 1995 Budget Request sufficient to implement the planned growth of the Branch? If not, what additional funding is needed?

Dr. Alexander. The FY 1995 budget will allow the Perinatal Research Branch to operate at the FY 1994 level. To properly implement the planned growth of the Branch would require an additional $5.0 million for the contract that supports the Branch, and an additional $2.0 million for the NICHD intramural research activity.

HISPANICS AND NIH

Mr. Serrano: Dr. Alexander, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions.

First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Alexander: In addition to the usual channels targeted to minority populations, the NICHD Equal Opportunity Manager sends vacancy announcements to a colleague in San Juan, Puerto Rico and to an organization for professional Hispanics in New York. We also monetarily support the Society for the Advancement of Chicanos and Native Americans in Science. Vacancy announcements will be sent to the director of that organization. The NICHD Equal Opportunity Manager networks with Hispanic colleagues in the FDA and with a Hispanic Program director at the PHS who is familiar with the Hispanic Scholars program in the District of Columbia Public Schools system.

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Alexander: Of the total NICHD budget, 5.5 percent is directed specifically at Hispanic health issues.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Alexander: The NICHD has been supporting minority supplements for research grants since 1989, with nearly $2.0 million as the current annual amount. Hispanic investigators make up a significant number of the investigators that are supported under this program.

Mr. Serrano: Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Alexander: We respond to supplement initiatives (Office of Research on Minority Health and Office of Research on Women's Health) by nominating appropriate funded applications for supplemental funding targeted toward minority subject recruitment. In addition, the NIH guidelines on the inclusion of women and minorities as subjects in clinical research, among other things, require that NIH must (a) ensure that women and members of minorities and their subpopulations are included in all human subject research, (b) for Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished, (c) not allow cost as an acceptable reason for excluding these groups and (d) initiate programs and support for outreach efforts to recruit these groups into clinical studies. The inclusion of minority subpopulations has particular importance for Hispanics.

The NICHD Trial of Calcium for Preeclampsia Prevention (CPEP) is the largest clinical trial ever undertaken to examine whether supplemental calcium administered to pregnant women will reduce their likelihood of developing preeclampsia and other hypertensive disorders of pregnancy. In the United States about one-fifth of all maternal deaths and one-fifth of all infant deaths are associated with maternal preeclampsia or hypertension.

In order to increase the number of Hispanics recruited into this trial, one of the five medical centers selected to enroll and monitor patients was the University of New Mexico School of Medicine in Albuquerque. About two-thirds of the patients enrolled into the trial at this medical center are of Hispanic origin. In Albuquerque a network of research clinics was established in public health facilities located in areas with large numbers of Hispanic residents. In order to make participation in the study more attractive to Hispanics as well as to increase the accuracy of information obtained from these patients NICHD has required Spanish-speaking nurses to be hired at Albuquerque and at the Oregon Health Sciences University in Portland, where a substantial minority of Hispanic patients are recruited. Overall at the 5 medical centers about 20 percent of patients recruited for the trial are of Hispanic origin. More than 95 percent contribute data to the study throughout their entire pregnancy.

As you know, HIV/AIDS is a fatal disease which is disproportionately affecting minority populations of women and children in the United States. The Final Report of the Secretary's Work Group on Pediatric HIV Infection and Disease noted that, while Hispanic children make up 10% of the pediatric population of the United States, 22% of childhood AIDS cases occur in children of Hispanic origin. Since the development of the NICHD HIV Clinical Trials Network, great care and attention has been directed to assuring minority children have access to the state-of-the-art of care and research that clinical trials represent. We have chosen our clinical trials sites carefully to assure geographic access to clinical trials. Within the trial units themselves, we have provided resources to investigators which are targeted toward reducing the barriers which prevent minority access to clinical trials. We are pleased to report to the Committee that our efforts in HIV clinical trials have met with success: 42% of our HIV/AIDS clinical trials participants are of Hispanic origin. We remain committed to recruiting and retaining participation of Hispanic children in HIV-related clinical trials.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Alexander: Because ethnic information is self-reported on grant applications, and available data is too limited on the NICHD, we cannot derive a meaningful answer to this question.

CENTER FOR POPULATION RESEARCH

Mr. Serrano: Dr. Alexander, I was interested in the description in the NICHD budget justification of behavioral research on violence and violent behavior in youth. Would you expand on that research for us?

Dr. Alexander: In late 1992, we initiated a set of cooperative agreements to develop, implement and evaluate community based health behavior interventions focusing on strategies for decreasing violence-related injuries and deaths, sexually transmitted diseases (STDs) and unwanted or unintended pregnancies in minority youth ages 10-18. The goals for these interventions reach beyond the delivery of information to help young people develop and practice skills in decision making, conflict resolution, and reducing their own risks of unhealthy outcomes. The projects involve collaborations between community-based groups and organizations and university-based researchers in both the design and the implementation phases. The Office of Research on Minority Health is providing the funding for this NIH initiative and the National Institute of Child Health and Human Development (NICHD) is managing the 5-year program.

Mr. Serrano: Dr. Alexander, I was also interested in the studies on illegal immigration from Mexico and its health impact. Would you expand on the findings and the further work that must be done in this area? In your professional judgement, should a U.S. health care system providing universal coverage cover undocumented persons?

Dr. Alexander: NICHD has supported research on the Mexico-United States migration process for the past decade. One study finds that the Immigration Reform and Control Act (IRCA) had little effect on illegal immigration to the United States, but has increased demand for U.S. social services, as the 5-year moratorium on service eligibility for the millions of former undocumented migrants granted amnesty under the Act has come to an end. Other research supported by the Institute has focused on the health of Hispanic immigrant families and children. Recent migrants have better than expected outcomes with respect to infant birth weight, infant mortality and many chronic diseases. However, as they assimilate infant outcomes deteriorate and the prevalence of chronic diseases increases. A new set of studies to be funded this year will extend this research by examining assimilation processes and their effects on child health within U.S. Hispanic populations. Future research initiatives will focus on the immigration process in Hispanic and other immigrant groups.

Any decision concerning the coverage of undocumented persons under health care reform will need to take into account the availability of alternative sources of health care available to such persons, their health status and health care needs, and the ability to enforce a decision to exclude them from coverage. Undocumented immigrants tend to be young, healthy and employed; however in some cases they are at higher risk for infectious diseases such as AIDS and Tuberculosis.

CALCIUM SUPPLEMENTATION/OSTEOPOROSIS

Ms. DeLauro: Your budget justification indicates NICHD is currently funding a clinical trial to determine the effects of calcium supplementation on bone density in adolescent girls. Given the terrible problem of osteoporosis in older women, I am very interested in this research. What can you tell us about what you have learned from this study so far, and how long will the study last -- will you try to follow these young women well into adulthood to see how protective early calcium supplementation and its attendant bone density buildup can be?

Dr. Alexander: Calcium plays a vital role in many biological functions including skeleton formation. The NICHD recently supported a randomized, double-blind, placebo-controlled clinical trial to determine the effects of oral calcium supplementation on bone density in adolescent girls. Results show that a daily supplement of 500 mg of calcium citrate malate increases the rate of acquisition of bone. The supplemented group compared with the placebo group gained 24 grams more of bone during the 24-month trial and had greater increases of lumbar spine bone density, lumbar spine bone mineral content, and total body bone mineral density. At this rate, the supplemented girls would have 6 percent greater bone density by age 18, which would provide protection against osteoporotic fractures later in life. These findings demonstrate that increasing daily calcium intake from 80% of the recommended daily allowance to 110% during adolescence can increase peak bone density and may prevent future osteoporosis and bone fractures.

The project will remain active through November 30, 1994. Results of the present study raise important questions concerning retention of effect and long-term benefit. Additional studies will be required to define the range of ages during which calcium supplementation is effective. Whether the gain in bone density and bone mass noted in this study will result in increased peak bone mass can only be answered when the girls reach skeletal maturity. Since other studies have shown that hip fracture rates are significantly decreased in adult populations who differ in peak bone mass by only six percent, the amount of extra bone gained by the supplemented girls in this study may provide significant long-term benefits. The investigators plan to follow this group of 91 girls as long as is practicable; however, no funds have yet been committed to this goal beyond November of this year.

ENDOMETRIOSIS RESEARCH

Ms. DeLauro: The FY 1994 Appropriations Bill Senate Report stated the Committee's concerns that little is known about the causes and natural history of endometriosis and fibroid tumors. Therefore, "...the Committee has provided sufficient funding within the budget of NICHD to significantly increase its research on endometriosis and fibroid tumors." I am very concerned about this because women with endometriosis suffer tremendous pain, and it is found in up to one-half of women who undergo surgery for infertility. How much was spent on endometriosis and fibroid tumors research in FY 1993? How much will you spend in FY 1994 and how much do you anticipate spending in FY 1995?

Dr. Alexander: In FY 1994 NICHD spent $1,864,000 on research on endometriosis and fibroids. Funding estimates for FY 1994 and 1995 are $1,970,000 and $2,070,000, respectively.

MALE INFERTILITY

Ms. DeLauro: To date, most infertility research and treatment has focused on women, yet 40% of human infertility is associated with male factors. Our current understanding of the causes of male infertility is quite poor. I understand the NICHD recently held a workshop on this issue and is developing an initiative on unexplained male infertility designed to accelerate research into this area. What areas of research do you anticipate this initiative will include? When will this initiative be finalized, and when do you expect the research could begin?

Dr. Alexander: The workshop on male infertility entitled "A New Look at Spermatogenesis", held March 15-16, 1993, provided concept guidance regarding male infertility research recommended for further emphasis. The priority was to promote basic or clinical research projects investigating the etiology and pathophysiology of infertility in the otherwise endocrinologically normal male for which the underlying cause of the interference with spermatogenesis is unknown.

The areas of research expected to be pursued would include efforts to detect subtle sperm function defects not now being detected; the effects on fertility of immune sequelae following transient insults; physiological insult resulting in testicular dysfunction and subsequent impaired spermatogenesis; defective sperm-egg interaction; or genetic abnormality manifested as early embryo loss.

The initiative has already been finalized and the availability of funding for this research area was announced by the NICHD with a Request for Applications with an application receipt date of May 18, 1994. The earliest anticipated date of award for the projects is December 1, 1994.

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES

Ms. DeLauro: The FY 1994 Appropriations Bill Senate Report stated "...within the increase provided for NICHD, the Committee believes that the efforts of the mental retardation research centers should be expanded." How much was spent on mental retardation and developmental disabilities research in FY 1993? How much will you spend in FY 1994 and how much do you anticipate spending in FY 1995?

Dr. Alexander: The funding levels for research on mental retardatation and developmental disabilities research are as follows. FY 1993 - $53,021,000, FY 1994 - $54,700,000, FY 1995 - $56,700,000.

NATIONAL EYE INSTITUTE

FINANCIAL MANAGEMENT PLAN

Mr. Smith. As NIH reviews the financial management plan developed in 1990, what modifications do you believe should be made?

Dr. Kupfer. The National Advisory Eye Council has expressed the opinion that NIH should drop or phase out the requirement that the average length of competing RPGs not exceed four years. More flexibility is needed at the Institute level to deal with specific portfolio management issues. In addition, a strong argument can be made that the four-year mandate tends to increase, not decrease, average costs, and that it decreases productivity as a result of more scientists having to spend valuable time writing and reviewing grant applications.

SUCCESS RATES

Mr. Smith. Your success rates have been dropping from historically high levels. Is this related to the number of clinical trials you are currently supporting?

Dr. Kupfer. Support for clinical trials has stabilized in recent years at about 11-12 percent of the total NEI budget, and has not been a factor in the decline in success rates. Because of the many exciting opportunities in vision research, NEI is receiving more competing grant applications now than at any other time in its history. However, between FY 1987, the high-water mark for the Institute, and FY 1993, expressed in constant dollars, NEI's funding has dropped by 4.1 percent, while the average cost of a competing grant did not change. These two factors, an increase in the number of competing grant applications and a decrease in purchasing power have combined to limit the percentage of applications which NEI can fund.

DOWNSIZING

Mr. Smith. Dr. Kupfer, you have a reputation as a good manager. What suggestions do you have for downsizing NIH staffing, as the Department-wide ceilings require?

Dr. Kupfer. The NIH has undergone streamlining in FY 1994. The budget for FY 1995 calls for more of the same and the outlook through FY 1999 is predictable if the current budget climate holds. The NEI, to reach the reduced FTE levels, has elected not to hire additional staff to fill several vacant positions. The workload from these unfilled positions has been reallocated and shared among other staff members.

DIABETIC EYE DISEASE REAUTHORIZATION PROVISION

Mr. Smith. How are you responding to the provision in the NIH reauthorization encouraging you to award grants in diabetic eye disease research, including the provision of equipment?

Dr. Kupfer. Research on diabetic retinopathy is of high priority to NEI, as established in consultation with the National Advisory Eye Council in our formal program planning process. The most promising opportunities for research and how these activities should be supported are addressed in Vision Research-A National Plan: 1994-1998, which has been widely distributed in the vision research community. The NEI and the Juvenile Diabetes Foundation International have initiated a cooperative program for research on diabetic retinopathy.

Mr. Smith. Do you plan to issue a request for applications or program announcement?

Dr. Kupfer. This program was announced recently in the NIH Guide for Grants and Contracts, and seeks to stimulate basic cellular and molecular research on diabetic retinopathy.

EYE DISEASE SPENDING

Mr. Smith. Identify projected FY 1993-1995 spending for the following: retinitis pigmentosa, glaucoma, diabetic retinopathy, macular degeneration, cataract, and CMV retinitis.

	Fiscal Year (Dollars in thousands)		
	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
Retinitis Pigmentosa	18,663	19,633	20,352
Glaucoma	24,285	25,547	26,482
Diabetic Retinopathy	13,577	14,283	14,805
Macular Degeneration	60,239	63,370	65,690
Cataract	20,144	21,191	21,967
CMV Retinitis	4,749	4,996	5,179

RESEARCH CENTERS

Mr. Smith. Identify the number, type, and subject matter of all research centers supported in FY 1994.

Dr. Kupfer. We estimate that NEI will support 30 Center Core Grants (P30) in FY 1994, 8 competing and 22 noncompeting. The objective of these grants is to enhance or facilitate the research efforts of a core group of investigators who already hold independent NEI grant support. Support for specific research projects is not provided. Instead, core grants support services or resources that would be impractical or undesirable to support on an individual research project grant. This can also include the purchase and support of a shared instrument. Core grants can be, and are, awarded to support groups of investigators in all areas of vision research--there are no restrictions in terms of subject area.

GLAUCOMA

Mr. Stokes. What are some of the more promising basic and clinical research opportunities in glaucoma?

Dr. Kupfer. The most prevalent form of glaucoma is primary open angle glaucoma (POAG), a form most common in people over 60. Even though genetic patterns of this form of the disease have been noted, the relative influence of genetic and environmental factors is unknown. As with many diseases in which the onset occurs late in life obtaining large families to test genetic factors is problematic. One form of the disease, juvenile glaucoma, is known to be inherited. Like POAG, juvenile glaucoma is characterized by elevated intraocular pressure. However, unlike POAG, onset occurs in early adulthood which makes a genetic analysis feasible.

Mr. Stokes. To what extent will they be pursued at the FY 1995 budget request level?

Dr. Kupfer. A number of studies are currently underway to identify the "glaucoma" gene responsible for juvenile glaucoma. Families in Michigan, New England, and Iowa have been identified. Recently, the disease-associated gene has been mapped to chromosome 1. Corroborating data from different labs using different families have confirmed this location and work to find its exact location is progressing.

Recently, researchers have been identifying families in which POAG is clearly inherited. By identifying genes associated with various forms of the disease, the underlying defects that result in vision loss due to glaucoma can be elucidated.

DECADE OF THE BRAIN

Mr. Stokes. Dr. Kupfer, what are some of the most recent and most important advances in neuroscience that offer tremendous opportunity for advances in the treatment, prevention, and early detection of eye diseases and disorders?

Dr. Kupfer. Recent NEI research priorities and opportunities in visual neuroscience include: the cellular and molecular mechanisms underlying the development and regeneration of the nervous system, the neural basis underlying eye movement disorders, the mechanisms at work during infancy which lead to visual perception problems in later life, the basis for degeneration of nerve tracts in the brain such as the optic nerve in glaucoma, the retina-mediated process involved in the development of nearsightedness, the role of growth factors in the rescue and repair of nerve cells in retinal degeneration, and the role of the immune system in a variety of neuro-ophthalmological disorders. This research could lead to transplantation of portions of the eye, regeneration of the retina to overcome blindness, and prevention of severe visual disorder such as strabismus and amblyopia that affect as many as 4 percent of all children.

Mr. Stokes. We hear a lot about the Neurology Institute's and the Mental Health Institute's involvement in the Decade of the Brain research initiative, but not very much about the Eye Institute's involvement in this initiative. What is the extent of the Eye Institute's involvement in the Decade of the Brain initiative at the NIH?

Dr. Kupfer. Since it's inception, the NEI has been playing a significant role in cultivating the growth of neuroscience research and continues this focus in its Decade of the Brain research. The NEI, ranked third among the NIH institutes in terms of monetary support provided for fundamental neuroscience, supports many outstanding neuroscientists working on the visual system. The potential rewards from visual neuroscience are great because the visual system affords a superb model at all levels of information processing, from signal transduction to central visual processing and motor control by the brain. The visual system has long been the subject of investigations that have been at the forefront of progress in elucidating the overall structure and function of the nervous system.

COST BENEFIT OF CLINICAL TRIALS

Mr. Stokes. What are some of the Eye Institute-supported clinical trials that have yielded the most in terms of cost benefits? To what do you attribute the cost benefit success of NEI-supported trials?

Dr. Kupfer. Clinical research conducted and supported by the NEI has been and remains extremely cost effective. One of the most beneficial areas of NEI clinical research in terms of cost benefits has been studies directed toward the treatment of diabetic retinopathy. NEI clinical research on diabetic retinopathy has cost the American taxpayer $181 million in 1992 prices, but is yielding annual societal savings of $1.2 to $1.6 billion. NEI's Diabetic Retinopathy Study and the Early Treatment of Diabetic Retinopathy Study demonstrated that laser treatment could prevent blindness in 95 percent of diabetic retinopathy patients. The cost of blindness includes Social Security benefits, lost income tax revenues, and Medicare expenditures.

RESEARCH PROJECT GRANT SUPPORT

Mr. Stokes. According to the Congressional Justification, the National Eye Institute would support 947 research project grants in FY 1995. This compares with 960 in FY 1994, and 975 in FY 1993. Would you translate for us what this ongoing decline in the number of research project grants supported means in terms of any limits it might place on opportunities for improving the quality of life?

Dr. Kupfer. The NEI devotes proportionately more of its extramural resources to R01-type, traditional research project grants, than does any other Institute at NIH, about 82 percent compared to about 58 percent for NIH overall. NEI does not award any program project grants at present or any other type of "umbrella" mechanism of research support. NEI devotes only about 3 percent of its resources to Center grants compared to about 12 percent for the NIH overall - and within the Centers line, NEI awards only Core grants which support shared resources and equipment - but not research per se. Research and development contracts make up only about 2-3 percent of the NEI portfolio. Thus, a decrease in the number of research project grants will have a relatively greater affect on NEI programs.

GENE THERAPY

Mr. Stokes. Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In the National Eye Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy? Elaborate briefly.

Dr. Kupfer. In recent years, with the explosion in molecular genetics, research by NEI scientists has lead to the identification of the genes involved in many inherited human ocular diseases. These include both retinitis pigmentosa and macular degeneration, diseases in which there is devastating visual loss and no effective treatments available. As a result, the promise of gene therapy is now emerging as a reality in the treatment of these diseases. The opportunity is here to explore the approaches and technologies for the application of gene targeting strategies in the search for new clinical therapies for patients with devastating eye diseases. To pave the way for human gene therapy, NEI researchers are developing gene transfer methodology in animals models of the diseases. This includes development of adenoviral vector-mediated gene transfer technology for the eye.

Mr. Stokes. How much is included in the FY 1995 budget request for gene therapy?

Dr. Kupfer. A total of $8.6 million is included in the NEI's FY 1995 budget request for gene therapy.

Mr. Stokes. How much did the National Eye Institute invest in this research in FY 1994 and FY 1993?

Dr. Kupfer. The NEI is investing $8.3 million in gene therapy in FY 1994. In FY 1993, the NEI invested $7.9 million.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes. I understand that a number of Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place?

Dr. Kupfer. The NEI began reporting on the supplement program in FY 1990.

Mr. Stokes. How many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Kupfer. No minorities that have successfully completed the supplement program have as yet received a research award from the NEI. One minority investigator has submitted a FIRST (R29) Award application which will be reviewed at the October, 1994 meeting of the National Advisory Eye Council.

MINORITY HEALTH CRISIS

Mr. Stokes. As the Director of an institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement: "The minority health crisis continues--while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and--while medical and technological breakthroughs are affording Americans a longer life expectancy"? Please elaborate.

Dr. Kupfer. I believe we need to find ways of applying the advances of biomedical research and technology development to assess not only effective treatments and therapies for various diseases and disorders but also to identify individuals who are at the greatest risk from these maladies. For example, an NEI-supported study found that African Americans are four to five times more likely to develop open-angle glaucoma than Whites. This finding provides the most conclusive evidence to date that African Americans are at higher risk than Whites for the disease. The study also found that African Americans develop open-angle glaucoma earlier, around age 40, than whites and that the disease tends to progress more rapidly in African Americans. By age 70, one in eight African Americans have open-angle glaucoma, compared to one in fifty Whites. By understanding more precisely the magnitude of the problem, the NEI and other vision research organizations are able to adopt appropriate strategies aimed at controlling the disease in the African American community. That is why our National Eye Health Education Program has concentrated on reaching people at risk for glaucoma particularly African Americans over the age of 40 and everyone over the age of 60.

PROMISING BASIC RESEARCH OPPORTUNITIES

Mr. Stokes. What are some of the most exciting and most promising basic research opportunities at the National Eye Institute? Elaborate on the benefits to be achieved from further investments in this research.

Dr. Kupfer. (1) The location of genes to specific chromosomes is the first step in uncovering the basis of genetic diseases. For macular degeneration, where there are no animal models available, molecular genetics offers some hope for future understanding of this disease as well as guiding approaches to therapy. The location of the gene responsible for North Carolina Macular Dystrophy to a specific region of chromosome 6 and the location of the Best's disease gene to chromosome 11 are specific examples.

The mutation or defect in at least two genes that cause some forms of retinitis pigmentosa (RP) have been discovered. Scientists are now trying to understand how defects in these genes cause disease. Understanding the molecular mechanisms of different forms of RP is critical to the development of strategies for clinical therapy.

(2) Special structural proteins called crystallins are a major component of the lens of the eye and contribute to its transparency. One of these crystallins has been found to play a role as a molecular "chaperone" in guiding the assembly of large molecular structures. With this basic knowledge, it is now possible to investigate long-standing questions about lens biology and the formation of cataracts.

(3) Glaucoma is a heterogenous group of eye disorders which share a distinct type of optic nerve damage that can lead to blindness. Manufactured drugs have long been the front line armamentarium in the treatment of this disease. With the discovery of a natural compound that lowers intraocular pressure, called a prostaglandin, it has been possible to modify this molecule in such a way so as to make it specific and effective as a possible therapeutic agent. Another naturally occurring molecule called nitric oxide has been identified which is involved in the regulation of fluid production in the eye. Knowledge of how this molecule performs its function will lead to a better understanding of how it regulates itself, with implications for therapeutic intervention.

(4) The regeneration and repair of the visual system has implications for treatment of disease and restoration of sight. Critical to understanding the regenerative process is a knowledge of the factors that control the elongation and guidance of visual nerve axons. Research over the last decade shows that adult visual neurons do not synthesize all the constituents that they did during their development. A class of molecules known as "GAPs" are found in the developing central nervous system but are not made by cells once development ends. Recent work shows that experimental interruption of optic nerves can lead to a new wave of GAP production. In the

future, investigators will try to find what factors regulate GAP production with the goal of enhancing the regenerative capacity of the visual system.

(5) Eye researchers have shown that molecules called "oncogenes" are important in formation of the lens. Oncogenes in normal cells play the role of a master switch, turning genes on and off. In experiments with genetically altered mice, it has been shown that inhibition of oncogenes in the lens results in abnormal eye formation. Researchers hope to be able to discover what specific genes are controlled by the oncogenes.

PIPELINE OF TRAINED RESEARCHERS

Mr. Stokes. For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your institute?

Dr. Kupfer. The outstanding progress in every field of vision research from molecular biology to the psychology of vision has been made possible by the existence of a cadre of laboratory and clinical scientists that are well trained and dedicated to the problems of visual disorders. To maintain this strong vision research establishment, the NEI is committed to recruiting, training and developing a future group of researchers, which includes fostering opportunities for women and minority groups. Through grants to institutions and individuals, NEI is enhancing training in scientific disciplines, such as molecular biology and immunology, to ensure that adequate numbers of vision scientists will be both available and trained in the latest technologies. In addition, NEI strongly encourages and supports the FIRST AWARD program and Physician Scientist Award as opportunities for new investigators. Programs of support in specific training in visual sciences at the graduate and postdoctoral level must convince students that their perseverance and dedication will be rewarded with opportunities for productive careers and support for their research endeavors. Therefore, vision research must be supported with high priority placed on individual investigator-initiated project grants.

PROMISING CLINICAL RESEARCH OPPORTUNITIES

Mr. Stokes. What are some of the most exciting and most promising clinical research opportunities at the National Eye Institute? Elaborate on the benefits to be achieved from further investments in this research.

Dr. Kupfer. There are a number of new ideas for clinical research which could be pursued if sufficient funds were available. Examples include studies of congenital esotropia that would determine the effectiveness of treatment with crystallized botulinum toxin versus surgery for this condition; a study of the efficacy of vision training in a very prevalent disorder, intermittent exotropia; a clinical trial to evaluate surgical removal of subfoveal choroidal neovascularization secondary to age-related macular degeneration, ocular histoplasmosis, or idiopathic causes; a study to evaluate the visual benefit of surgery for macular holes and hemorrhagic macular degeneration; a study of the natural history of a large cohort of keratoconus patients to evaluate the progression of the disease and its relationship to contact lens wearing and type of lens worn; and, a study designed to gather natural history data on patients with dry eye, to assist in refining the definition of the dry eye syndrome, and to identify potential treatments for clinical trial investigations.

MINORITY RESEARCH AND RESEARCH TRAINING

Mr. Stokes. Please describe the measures the National Eye Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Kupfer. The NEI has research and education programs specifically directed at glaucoma, which has a higher prevalence and occurs at an earlier age in African Americans than in Whites, and diabetic retinopathy, which has a higher prevalence in Hispanics than in the general population. Principal investigators and minority applicants who contact the NEI are made aware of the fact that these diseases disproportionately affect minority populations. Additionally, NEI staff attend workshops and conferences and encourage researchers to address these areas.

INITIATIVES IN MINORITY HEALTH

Mr. Stokes. What significant initiatives in minority health research and research training, and outreach are supported by the National Eye Institute?

Dr. Kupfer. The National Eye Health Education Program (NEHEP), coordinated by the NEI, provides technical assistance nationwide to organizations interested in developing glaucoma or diabetic eye disease education programs, particularly among minority groups and other underserved populations. The initial target audience for glaucoma education programs are African Americans over age 40, who are at highest risk for developing the disease, and everyone over the age 60. The target audience for the diabetic eye disease education programs are everyone with diabetes. Over 32,000 education kits, which contain a variety of resources, have been distributed to community educators, health professionals, and pharmacists.

Three health education research projects on diabetic eye disease are being supported. These project are evaluating various education strategies designed to reach people with diabetes about the importance of getting annual eye examinations. One project is directed to Native Americans, another reaches low-income African Americans, and the third targets all people with diabetes.

Several glaucoma clinical trials, with very large proportions of African Americans in the study populations, have just begun. The first is to study individuals who have not yet developed frank glaucoma--that is, loss of visual function, but who do have elevated pressure in the eyes. These individuals are at high risk to develop glaucoma and loss of visual function. The second trial will focus on determining the best treatment for newly diagnosed glaucoma. Should we continue to give medicine and try to control pressure medically, or should we have as a primary intervention a surgical procedure which due to many research advances is much safer than it was two decades ago? Surgery may not only make unnecessary the continual use of medicine every day, but might even have a more beneficial effect on reducing the pressure in the eye and therefore retarding the progression of the disease.

PRIORITIES FOR MINORITY RESEARCH AND RESEARCH TRAINING

Mr. Stokes. How does the National Eye Institute identify its priorities for investments in minority research and research training?

Dr. Kupfer. The NEI programs are guided by a long range plan, established in consultation with the National Advisory Eye Council. A number of important opportunities for research on minorities and research training are addressed in Vision Research-A National Plan: 1994-1998, copies of which have been widely distributed in the vision research community. NEI program directors are in contact with minority investigators and are available to assist them by providing advice on application procedures and program priorities. The NEI and the National Advisory Eye Council have placed a high priority on the trans-NIH Initiatives for Underrepresented Minorities in Biomedical Research. This program provides administrative supplements to research grants for the support of underrepresented minority scientists and students. The aim of this program is to attract and encourage minority individuals to pursue careers in vision research.

NIH OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes. When the Office of Research on Minority Health provides funds to the National Eye Institute, do these funds typically augment existing minority programs or efforts, or do they replace funds your institute previously invested in its minority research and research training initiatives? Elaborate.

Dr. Kupfer. Funds provided to NEI by the NIH Office of Research on Minority Health (ORMH) have typically been used to augment existing minority programs or efforts. For example, such funds recently enabled NEI to fund additional participating clinics for the Ocular Hypertension Treatment Study (OHTS). Funds from the

ORMH were used to support the participating clinic at King Drew Medical Center in Los Angeles, which has an African American as the principal investigator and which is expecting to recruit more than 70 percent of its participants from the East Los Angeles area. Funds received from ORMH were also used to support the OHTS clinic at the University of California at San Francisco, which also has an African American as the principal investigator and which is targeting the recruitment of African Americans and Asian Americans from the Bay area. Additionally, some of the funds from the ORMH were used to develop outreach materials and recruitment strategies aimed at the inclusion of African Americans and other minority groups in this clinical trial.

Mr. Stokes. When your institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health? To what extent is there a collaborate relationship between the two organizations? Elaborate.

Dr. Kupfer. NEI staff and staff of the Office of Research on Minority Health frequently discuss matters of mutual interest. These discussions generally involve NEI's Division of Collaborative Clinical Research and the NEI Research Resources Officer who has been given lead responsibility for coordinating a number of minority research-related activities within NEI and with other NIH components. The co-funding agreements between NEI and ORMH have served to enhance these collaborations.

CLINICAL TRIALS

Mr. Stokes. How much is included in the FY 1995 budget request for clinical trials?

Dr. Kupfer. Including all mechanisms of support, approximately $26.4 million (non-AIDS) is included for clinical trials in the NEI FY 1995 budget request.

Mr. Stokes. How does this amount compare with the amount invested in clinical trials in FY 1994, and FY 1993?

Dr. Kupfer. This compares to $25.3 million in FY 1994, and $24.4 million in FY 1993.

Mr. Stokes. Would you please comment on the economic benefits, and the quality of life benefits of the some of the major clinical trials supported by the National Eye Institute?

Dr. Kupfer. NEI supported clinical trials can be demonstrated to be extremely cost effective. Laser photocoagulation for treatment of retinopathy is estimated to save between $1.2 and $1.6 billion each year by reducing the risk and costs of vision loss. It is estimated that full implementation of the study results can preserve the useful vision of more than 30,000 working-age Americans each year.

Mr. Stokes. To what extent has the National Eye Institute increased the number of minorities participating in its clinical trials. What progress is being made?

Dr. Kupfer. The number of minorities participating in NEI supported clinical trials is increasing rapidly and will continue to increase in the future. Two new clinical trials on glaucoma, for example, will be recruiting large numbers of African Americans, a group affected disproportionately by this disease.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes. What are some of the major initiatives underway at the National Eye Institute to increase the participation of historically black colleges and universities in biomedical research?

Dr. Kupfer. (1) The NEI, where possible, has tried to link vision research investigators at minority institutions with those at majority institutions. (e.g., Meharry Medical College with Vanderbilt University).

(2) The Institute has been active in the recruitment of HBCU investigators at national minority meetings to vision research and encouraging them to submit appropriate grant applications to the National Institutes of Health.

(3) Principal investigators with NEI-funded grants at HBCU institutions have been advised to consider the submission of applications for minority supplements to those grants.

NEI PERSONNEL

Mr. Stokes. How many GS-15 and above positions are there in the National Eye Institute?

Dr. Kupfer. There are 31 NEI positions at the GS-15 and above level.

Mr. Stokes. How many employees in the National Eye Institute are in GS-15 and above positions?

Dr. Kupfer. There are 28 NEI employees at the GS-15 and above level.

Mr. Stokes. In the National Eye Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they?

Dr. Kupfer. There are no African Americans at the GS-15 and above level.

Mr. Stokes. In the National Eye Institute how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Kupfer. There are no African Americans among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level.

Mr. Stokes. Has the NIH requested relief from the freeze? If so, what was the response?

Dr. Kupfer. The NIH has requested relief from the freeze, but has not yet received it.

Mr. Stokes. If the freeze were lifted, how would it help the EEO problem in the National Eye Institute?

Dr. Kupfer. If the hiring freeze were lifted, the NEI would be able to recruit for vacancies outside of the Public Health Service and we would be able to reach a broader range of people, including targeting minority colleges and institutions.

HEALTH PROMOTION AND DISEASE PREVENTION

Mr. Stokes. With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at the National Eye Institute?

Dr. Kupfer. The primary goals of NEI prevention initiatives are to identify the molecular defects associated with the development of blinding eye diseases, as well as systemic, immunologic, biochemical, and/or environmental factors that contribute to their development. Clinical and laboratory scientists will use this knowledge to develop screening techniques, gene therapy, clinical treatments, or pharmacological approaches aimed at preventing disease or its blinding consequences. Specific areas that the NEI is focusing on include: the prevention of retinal and macular degenerative diseases; development of aldose reductase inhibitors for the prevention of diabetic eye disease; prevention or delay of age related cataract; and, identification and characterization of a "glaucoma" gene. Where highly effective treatments are currently available, such as in the case of diabetic retinopathy, the goal will be to expand our efforts in eye health education and expand our activities, including those directed at minority populations who may be at particular risk for blinding eye diseases. The prevention of blinding eye diseases and visual disorders will not only help more people to maintain healthy and productive lives, but will save society an estimated $22.3 billion in direct costs and $16.1 billion in indirect costs each year.

BIOTECHNOLOGY

Mr. Stokes. Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your institute.

Dr. Kupfer. The National Eye Institute's Biotechnology program has contributed greatly to the explosive development of new techniques and materials that are revolutionizing many aspects of biological science, medicine, and industry. Ultimately, the accelerated application of this technology will provide a detailed understanding of the visual system at the molecular and genetic level, and new methods to treat and prevent eye diseases and disorders.

Some key objectives of this program and new opportunities that could be pursued include the identification and testing of: growth factors to support the rescue and regeneration of nerve cells which have been damaged or destroyed by trauma or disease; biological inhibitors to prevent the sight-threatening formation of abnormal blood vessels in the eyes of patients with diabetes; drugs and biologics to prevent retinal detachment and the development of cataracts, to promote the healing of corneal wounds, and to treat glaucoma; and the development of new diagnostic methods to detect, and vaccines to prevent, herpes, trachoma, and other ocular infections.

SUPPORT FOR MINORITY INSTITUTIONS

Mr. Stokes. What is the present level of support provided to minority institutions by the National Eye Institute?

Dr. Kupfer. In FY 1993, the NEI provided $2.1 million to support minority institutions.

"CATCH 22" SITUATION FACED BY MINORITY INSTITUTIONS

Mr. Stokes. Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the institute's programs and activities?

Dr. Kupfer. Prospective principal investigators at HBCU institutions are being advised to use the Academic Research Enhancement Award (AREA) mechanism when submitting grant applications to the NEI since this award is designed to assist research-poor institutions to achieve entry into funding for biomedical research.

These applicants are encouraged to seek advice in preparation of such grant applications from the program directors at the NEI prior to submission of the applications to the Division of Research Grants at the National Institutes of Health for review.

PARTICIPATION OF UNDERREPRESENTED MINORITIES

Mr. Stokes. Explain the proposed funding for the programs of the National Eye Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training?

Dr. Kupfer. The NEI views the participation of underrepresented minority in biomedical research and research training, as a high priority. Specifically, the NEI is continuing to increase its activity in FY 1994 in the Research Supplements for Underrepresented Minorities Program. It participates in the Minority High School Student Research Apprenticeship Program and co-funds grants in the National Institute of General Medical Sciences' MBRS Program. NEI also participates in the Minority Predoctoral Fellowship Program. The NEI supports a small instrumentation grant and several vision research projects at the medical school of a Historically Black College in addition to providing support for vision research grants at other minority institutions.

The National Eye Institute is actively participating in the summer student program conducted by the NIH Equal Employment Office in the Warren Grant Magnuson Clinical Center that places promising minority students in research laboratories for the summer months.

Each organization which applies for a new institutional training grant to the NEI must provide specific plans for the recruitment and retention of underrepresented minorities in their training program. The NEI is also requesting that organizations which submit competing continuation applications of their training grants provide in their progress reports detailed accounts of their successes and failures in recruitment of individual minority students. Furthermore, the staff of the NEI Division of Collaborative Clinical Research is working with investigators at several minority institutions to enhance and expand their participation in clinical vision research activities. Recently, a minority medical school has received an NEI award to function as a cooperating clinic in the multi- center Ocular Hypertension Treatment Study (OHTS).

The NEI continues in FY 1994 to provide Minority Travel Fellowships to assist young minority scientists in attending the annual meeting of the Association for Research in Vision and Ophthalmology, the major organization of vision scientists in the United States.

With respect to funding, in FY 1993, additional funds were designated to support expansion, as well as new initiatives. A total of $16.0 million supported minority health research and research training. In FY 1994, $16.8 million is being provided and $17.5 million has been requested for FY 1995.

PLANNING PROCESS

Ms. Lowey. Your testimony emphasizes the National Eye Institute's ability to invest its resources in areas that are likely to yield major advances. Can you tell the Committee more about how your planning process enables you to make these determinations?

Dr. Kupfer. I believe that the key component of the planning process that the NEI has employed for over twenty years is that it draws on the expertise of the vision research community to assess the needs and make recommendations on where to invest the resources. The National Eye Advisory Council establishes panels of scientific experts that represent each of NEI's major programs to define the scope and impact of important research areas, to update program goals and objectives, to review current research support and recent scientific advances, and to determine key research questions to be addressed. The results of this effort are published in a document that the NEI uses to manage its research programs. The most recent of these planning documents is Vision Research--A National Plan: 1994 - 1998.

Ms. Lowey. Does your planning process differ from planning methods used by other Institutes?

Dr. Kupfer. Some of the institutes and centers at the National Institutes of Health approach planning in a manner similar to that of the NEI. The NEI's reliance on expertise of the scientific community keeps NEI programs current with recent scientific advances and also allows it to exploit emerging technologies that advance knowledge of the pathology and treatment of diseases and disorders of the eye and visual system.

Ms. Lowey. If so, should other Institutes adopt the approach to planning used by the NEI?

Dr. Kupfer. While the NEI believes its approach to planning works extremely well, each institute must consider the unique aspects of its mission, the resources available, and the special needs and opportunities in each of its program areas, as it develops and conducts its program planning activities.

COOPERATIVE EFFORT WITH JUVENILE DIABETES FOUNDATION

Ms. Lowey. I am interested in the $4 million cooperative effort the National Eye Institute is launching with the Juvenile Diabetes Foundation to encourage basic research into the specific causes of diabetic retinopathy, which causes blindness in approximately 100,000 Americans. Can you update the Committee on this initiative?

Dr. Kupfer. The NEI/Juvenile Diabetes Foundation International (JDFI) program on cooperative funding of basic research on the causes of diabetic retinopathy was recently initiated. Grant applications which are responsive to this program will be reviewed in about a month for scientific merit. The NEI and JDFI will be making funding decisions shortly thereafter.

HISPANIC RECRUITMENT AND PROMOTION

Mr. Serrano. Dr. Kupfer, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within the National Eye Institute.

Dr. Kupfer. The NIH had developed the Federal Equal Opportunity Recruitment Program (FEORP), with the objective of ensuring that the Federal work force reflects the diversity of the population which exists in the Nation as a whole. Accordingly, the National Eye Institute (NEI) has identified specific occupations that are underrepresented among women and minorities. When vacancies become available within these occupations, the supervisor, the personnel specialist, and EEO specialist discuss the recruitment possibilities, i.e., how to reach minority candidates. In addition, our managers and supervisors are committed to recruiting and hiring women and minorities in scientific training positions to increase the possibilities for selection into permanent positions.

HISPANIC HEALTH ISSUES

Mr. Serrano. Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Kupfer. The NEI is currently spending approximately $300K on studying the incidence of age-related maculopathy in Hispanics and non-Hispanics, and on eye health education activities targeted to Hispanics. In FY 1995, the NEI will continue to fund this grant and expand Hispanic health education. Funding will increase to approximately $350K, or .12 percent of the total budget.

HISPANIC PARTICIPATION IN BIOMEDICAL RESEARCH

Mr. Serrano. Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Kupfer. The NEI continues to participate actively in the trans-NIH Initiatives for Underrepresented Minorities in Biomedical Research by providing administrative supplements to research grants for the support of underrepresented minority scientists and students. The aim of this program is to attract and encourage minority individuals to pursue careers in vision research. Twenty-seven administrative supplements, totaling more than $819,000 were awarded in FY 1993 and this level is expected to increase in FY 1994 and

1995. Eleven of the 27 supplements were provided to support Hispanic individuals. NEI, in cooperation with the Association for Research in Vision and Ophthalmology, has initiated a competitive program that provides travel support for underrepresented minority graduate students and postdoctoral fellows to attend national scientific meetings. NEI co-funds grants in the National Institute of General Medical Sciences' Minority Biomedical Research Support Program, and is co-sponsoring a Request for Applications for Individual Predoctoral Fellowships for Minority Students.

HISPANICS IN CLINICAL TRIALS

Mr. Serrano. Fourth, what is the National Eye Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Kupfer. The NEI was instrumental in the development of and fully supports the implementation of the NIH policy requiring that women and members of minority groups, and their subpopulations be included in all NIH-supported biomedical and behavioral research projects.

Specifically NEI determines, during the review process for a Phase III clinical trial (a trial involving several hundred human participants), whether clinically important differences by ethnic group in the intervention are expected. If so, the trial must be designed to address these differences. For instance, if Hispanics and Whites are thought to respond differently to the intervention, the clinical trial must be designed to answer questions for each group. This means that an adequate sample size for each group must be recruited and retained. Cost as a barrier to recruitment and retention cannot be an issue. Should a trial not be able to meet these requirements, it cannot be funded.

Also, recruitment performance by ethnic group in NEI Phase III trials is monitored at least every six months by an outside oversight committee (Data and Safety Monitoring Committee). This group closely monitors the trial to determine if the trial as conducted will meet its objectives. In addition, investigators must report on an annual basis their recruitment and retention success. Future support of the project is determined based on the investigators' success in meeting recruitment goals.

Hispanics represent approximately 20 percent of the study population in NEI trials such as the Studies of the Ocular Complications of AIDS (SOCA) and the Silicone Study. The NEI is committed to enhancing the participation of minority populations in clinical research and fully supports the implementation of the new guidelines for the inclusion of women and minorities in clinical research. The NEI will continue to explore with our clinical investigators and community groups, opportunities to extend participation to Hispanic and other minority populations.

HISPANIC INVESTIGATORS

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates?

Dr. Kupfer. The PHS 398 application instructions request that the principal investigator provide information regarding date of birth, gender, race, and/or ethnic origin. A response is optional and is not a requirement for NIH consideration of the application. The data base, maintained by the Division of Research Grants, indicates that in FY 1993, NEI reviewed 14 applications submitted by Hispanic investigators, and awarded 4 of them, or a success rate of 28.6 percent, as compared to NEI's and NIH's overall success rates of 32.1 percent and 24.5 percent respectively. The NEI emphasis on Hispanic health in the National Eye Health Education program is expanding its outreach to the Hispanic research community. This could lead to pilot and demonstration projects in eye health services research directed at this community.

NATIONAL EYE HEALTH EDUCATION PROGRAM'S HISPANIC OUTREACH

Mr. Serrano. Dr. Kupfer in your statement, you tell us the National Eye Health Education Program (NEHEP) expansion to get the message on diabetic eye diseases out to Hispanics is "making excellent progress." Please describe how this program works. And is language the only difference from the existing program, or are there cultural and other changes that must also be made to assure the message gets through to the Hispanic community?

Dr. Kupfer. The NEHEP, coordinated by the NEI, is an interactive partnership with other organizations that are interested in eye health education and/or may represent various NEHEP target audiences. It is through this partnership that the NEI works to develop new programs on eye health education, including its new program for Hispanics. In developing a diabetic eye disease education program for Hispanics, language is just one factor that will be considered. Other issues, such as culture, the environment (acculturation), and socioeconomic factors, also will be addressed. To identify the most appropriate approaches to reaching Hispanics, the NEI staff is conducting the following activities: (1) identifying and consulting with experts and/or organizations representing the various Hispanic sub-groups including Puerto Ricans, Mexican-Americans, Cubans, and Central Americans; (2) conducting focus groups to learn more about the target audience's health knowledge, attitudes, and practices and to obtain information as it relates specifically to diabetes and diabetic eye disease; (3) establishing an ad hoc working group for Hispanic outreach to assist in planning a culturally sensitive education program and appropriate materials; (4) developing a communication plan to guide the development and implementation of the education program; (4) pretesting prototypes of materials with the target audience; and (5) producing and disseminating information to specific target audiences through appropriate channels in the Hispanic community.

EXPANSION OF THE NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. Bonilla. Last year I asked if the National Eye Health Education Program (NEHEP) produced educational materials in Spanish? Your answer was no. This year in your testimony you report that you have made excellent progress in expanding NEI's activities to alert Hispanics and you are proposing to "modestly expand" the eye health education program. What specific steps have been taken since we spoke last year and what will the modest expansion accomplish?

Dr. Kupfer. The NEI staff has developed an initial diabetic eye disease communication plan for Hispanics that addresses several key issues including language, culture, the environment (acculturation), and socioeconomic factors. To identify the most appropriate approaches to reaching Hispanics, the NEI staff will conduct the following activities this fiscal year: (1) identifying and consulting with experts and/or organizations representing the various Hispanic sub-groups including Puerto Ricans, Mexican-Americans, Cubans, and Central Americans; (2) conducting focus groups to learn more about the target audience's health knowledge, attitudes, and practices and to obtain information as it relates specifically to diabetes and diabetic eye disease; (3) establishing an ad hoc group for Hispanic outreach to assist in planning a culturally sensitive education program and appropriate materials; (4) developing a plan to guide the development and implementation of the education program; and (5) pretesting prototypes of materials with the target audience. We anticipate the program will be launched in the winter of 1994-95. We will continue to work closely with the NEHEP Partnership and other community-based organizations in disseminating diabetic eye disease information through appropriate channels in the Hispanic community.

Mr. Bonilla. How will the NEHEP expand its plan for next year to reach more Hispanics and Native Americans?

Dr. Kupfer. With the development of a diabetic eye disease program for Hispanics, we will be better prepared to support both national and local organizations in reaching this population at high risk for eye complications from diabetes. The NEI staff will involve the Hispanic community throughout the program planning process, thus increasing the likelihood of a successful program. We will work closely with the NEHEP Partnership and local organizations to disseminate information through appropriate community channels. This coordination of activities will help to ensure that consistent, effective messages reach the population at risk for diabetic eye disease. Local organizations interested in developing diabetic eye disease programs will be given technical assistance by NEI staff.

The NEI works closely with the Indian Health Service (IHS) to disseminate information through the IHS health clinics. New organizations and programs reaching Native Americans continue to be identified, as well as opportunities for future collaborations. Based on the available resources for next year, we plan to explore alternative health education strategies to reach Native Americans at risk for eye complications from diabetes. A planning process similar to that used in developing the Hispanic diabetic eye disease program will be conducted.

Mr. Bonilla. Does the NEHEP plan to support any Hispanic pilot programs like the two African-American programs in Durham, North Carolina and Cleveland, Ohio?

Dr. Kupfer. Evaluation will be an important component to the diabetic eye disease program for Hispanics. It is critical to identify and evaluate the effectiveness of strategies designed to reach the Hispanic community. The NEI staff will work closely with the NEHEP Partnership and the ad hoc working group for Hispanics to coordinate the development and implementation of a Hispanic pilot program similar to the one conducted through the National Medical Association, a member of the NEHEP Partnership.

DIABETIC RETINOPATHY

Mr. Bonilla. What affect will the proposed budget have on diabetic retinopathy? Is it still a high priority at NEI?

Dr. Kupfer. The NEI budget for diabetic retinopathy will receive a cost of living increase in FY 1995. This will allow for continued maintenance of the ongoing research program. Diabetic retinopathy is still one of the highest priorities of the NEI.

NATIONAL EYE HEALTH EDUCATION PROGRAM

Mr. Bonilla. Last year, Chairman Natcher asked what share of people with eye problems are reached by the National Eye Health Education Program (NEHEP). Could you update the subcommittee on this question?

Dr. Kupfer. The NEHEP has made significant progress in reaching people at risk for eye disease, this includes, for glaucoma, African-Americans over age 40 and anyone over age 60 and, for diabetic eye disease, all people with diabetes. We estimate that 60 percent of the target audiences at risk for these eye diseases have been exposed to the NEHEP message on the importance of dilated eye examinations since the launch of the Program in December, 1991.

Specific accomplishments include:

a) The NEHEP Partnership has been expanded and now includes 52 public and private organizations. This partnership, representing over 500,000 community leaders and health professionals, provides the NEHEP the opportunity to effectively reach people at risk through eye health education programs conducted in their local communities.

b) Three education kits were developed and distributed. Over 32,000 copies of the *Glaucoma Community Education Kit*, the *Educating People With Diabetes Kit*, and the *Information Kit for Pharmacists* have been distributed. The kits include resources such as program guides, brochures, posters, and fact sheets, that can be used by community educators in reaching populations at risk.

c) A public service campaign on glaucoma and diabetic eye disease was produced. Television public service announcements on glaucoma were aired in 47 states, by over 300 stations, representing $2.7 million in public service time. Radio public service announcements on glaucoma were aired in 49 states by 400 stations, representing $700,000 worth of air time.

The NEI staff continues to identify new strategies to reach people at risk for diabetic eye disease or glaucoma. Through the structure of the NEHEP Partnership, we are able to reach people in the local community using familiar resources and programs thus increasing the likelihood that messages will be accepted. As the NEHEP continues to grow, we will need to be prepared to assess the long term effectiveness of our Program. To assist us in this process, an evaluation task force has been established to provide guidance to the NEI staff in the development of a plan that will measure both short and long term goals of the NEHEP. This plan will be particularly important in measuring the impact of the program as we move from increasing the awareness of eye disease to measuring behavior change over the next 10 years.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

PORTFOLIO BALANCE

Mr. Smith. Diabetes and nutrition seem to be two areas of your research that have received special Congressional interest. Have you been able to maintain a balance in your research portfolio while responding to this interest or are other disease areas suffering as a result?

Dr. Gorden. Fortunately, many exciting scientific opportunities have developed in diabetes and nutrition research during the past few years, and Congressional interest has enabled the NIDDK to pursue some of these opportunities while maintaining appropriate portfolio balance. The real key to generating such opportunities is a solid foundation of knowledge in basic science.

NUTRITION

Mr. Smith. Do you have any control over resources for nutrition research beyond those available to your Institute?

Dr. Gorden. Recently the Division of Nutrition Research Coordination and the NIH Nutrition Coordinating Committee were transferred to the NIDDK from the OD, NIH. Through leadership of these coordinating organizations, the NIDDK can promote the cooperative and efficient utilization of nutrition resources at the NIH. For instance, we are taking the lead to develop a trans-NIH initiative on an area of fundamental nutrition research that is of interest to most of the Institutes. A number of Institutes have indicated their willingness to participate in this Bionutrition Initiative and to contribute funds in support of the effort. Through this sort of activity, the NIDDK hopes to be able to encourage new investigators and established investigators from other fields to offer a fresh perspective to nutrition research. We also will encourage the NIH Institutes to utilize the Nutrition Coordinating Committee as a forum for the early discussion of their individual nutrition initiatives and activities. Such discussions can generate opportunities for joint initiatives and for collaborative funding of projects of mutual interest.

FIAU CLINICAL TRIAL

Mr. Smith. The clinical trial of the hepatitis B drug, FIAU, shocked the public with the rapid deaths of a number of patients. Although it is always known that a clinical trial carries some element of risk, is it unusual for patients to die in a clinical trial?

Dr. Gorden. It is unusual for patients to die during a clinical trial of treatment of chronic hepatitis B. Chronic hepatitis B by itself can lead to severe liver disease, cirrhosis and death. In other trials, a rare patient may be included with advanced disease who might die of the underlying disease during or shortly after the study. What was unusual in the study of FIAU was the number of deaths and the fact that they were due to the medication being studied rather than the underlying disease.

Mr. Smith. What investigations are underway or completed pertaining to the design of the trial and its conduct?

Dr. Gorden. The tragic deaths of several of the participants in this trial have caused immense anguish to all of us at the NIH. The NIH is committed to evaluating thoroughly the clinical experience with FIAU toxicity. The NIH Office of Human Subjects Research and the NIH Clinical Center's Quality Assurance program staff have already conducted reviews to determine whether NIH procedures were followed, and, based on analyses to date, they have concluded that they were. The NIH also established an independent, external review committee to look at all its studies of the experimental drug FIAU in humans. This review is being conducted by outside experts who are examining the totality of the studies performed by NIH investigators. The committee will report its findings and recommendations to the Advisory Committee to the Director, NIH, and to the NIH Director.

In addition, the Food and Drug Administration has released a special task force report on FIAU toxicity, which was intended to concentrate on hepatic and pancreatic damage associated with the study of this drug. It is our understanding that the focus of a second FDA investigation is whether the trial's sponsors and investigators were in compliance with existing FDA reporting requirements. The Assistant Secretary for Health has also requested the Institute of Medicine of the National Academy of Sciences to conduct a broader review of the entire group of human studies of FIAU. Results of NIH and FDA reviews will be made available to the IOM.

Finally, the Subcommittee for Human Resources and Intergovernmental Relations of the House Government Operations Committee is presently reviewing the deaths and other adverse events surrounding the FIAU trials. It is our sincere hope that the reviews I have outlined will lead us to understand as fully as possible the events that occurred relating to the FIAU clinical trial.

Mr. Smith. Has this experience led you to change your procedures for future clinical trials.

Dr. Gorden. The FIAU experience has led to a reassessment of all Phase I trials of therapies. Changes in processes await recommendations resulting from the reviews of the Advisory Committee to the Director, NIH, and of the Institute of Medicine.

FULL-TIME EQUIVALENT EMPLOYMENT

Mr. Smith. Your intramural staffing increases from 1993 to 1994, then drops again for 1995. What accounts for this pattern?

Dr. Gorden. The numbers are not comparable to each other. The 1993 number is an actual rather than a ceiling, while 1994 and 1995 are both ceilings. Inclusion of reimbursable FTEs and formerly exempt employees in the 1994 and 1995 figures creates the false appearance of an increase.

In actuality, NIDDK is undergoing a decrease of 16 directly appropriated FTEs in 1994, from 612 to 596. We have managed our hiring carefully, have eliminated several positions and have consolidated some offices. We will meet our target of losing 16 FTEs.

In 1995, we are scheduled to undergo a similar reduction of 18 FTEs. We will do our best to meet this target as well.

COMPETING GRANT AVERAGE COSTS

Mr. Smith. Why doesn't your 1995 budget provide any increase in the average cost of a new grant?

Dr. Gorden. Our figures give the appearance of a very large increase in average cost from 1993 to 1994, followed by almost no increase in average size from 1994 to 1995, as you have observed. These differences are due to our large clinical trials finishing together and new trials beginning in the competing column all in the same year, 1994.

NIDDK has finished the Diabetes Control and Complications Trial and the Modification of Diet in Renal Disease Trial on the same schedule. The results of these trials have indicated important new directions for clinical research, and the clinical trials funds are being used to conduct a new Type I Diabetes trial, a new Type II diabetes trial, a clinical trial of kidney disease and hypertension in African Americans, and a trial on morbidity and mortality in hemodialysis patients.

Three of these new trials are all entering their phase 3 stage in 1994, and their large individual award size has caused a large increase in the average size of competing awards. The average in 1995 will show no increase and may well fall as these clinical trial awards move to a noncompeting status, but all of the competing awards will receive the increase they are allowed under the NIH Cost Management Plan.

DIABETES CONTROL AND COMPLICATIONS TRIAL

Mr. Smith. Your recently completed Diabetes Control and Complications Trial showed that strict control of blood sugar levels can reduce major complications. Are patients likely to be able to maintain such strict controls without the discipline of a clinical trial?

Dr. Gorden. Perhaps the most important message of the Diabetes Control and Complications Trial (DCCT) is that even partial implementation of the DCCT's recommendations is beneficial to diabetic patients. The DCCT showed that intensive control of blood sugar levels prevented or delayed several of the complications of insulin-dependent diabetes, including eye, nerve, and kidney damage. Volunteers in the 10-year study "went for the gold." Their objective was to bring their blood sugar levels as close to normal as possible. They achieved this through multiple daily blood sugar tests and insulin injections. You are correct that the intensive regiment they followed was and is not easy, and achieving the gold standard they established can be a struggle.

Importantly, however, the DCCT showed that *any* improvement in blood sugar control reduced a person's risk of developing the complications that plague patients with this chronic disease. We must not overlook the DCCT's message to every patient who depends on insulin injections to survive: any improvement in blood sugar control enhances a person's chances of avoiding or delaying the diabetic complications that occur insidiously over years. An effort to control blood sugar, even if it is not "golden," can keep people with diabetes healthier.

MAJOR NIDDK CLINICAL TRIALS

Mr. Smith. How many clinical trials are you currently involved in? What impact has this had on the number of individual grants you are able to support? What is the total cost of the new non-insulin dependent diabetes prevention trial?

Dr. Gorden. With respect to major, multicenter clinical trials, the NIDDK is just finishing two such trials. Three new major clinical trials are starting the phase 3, or full-scale stage in 1994, and a fourth is involved in a prolonged screening phase involving large numbers of potential candidates. These trials are all awarded as cooperative agreements, and are therefore conducted with research project grant funds. Since most of the cooperative agreements are much larger than other types of awards, they represent a smaller number of awards than would be made if the same funds were used for other types of research project grants.

For example, in 1993 a total of 73 cooperative agreements were supported for a total of $31.7 million. If these funds had been used for other, smaller research project grants, an estimated 152 grants might have been supported, or 79 more than actually occurred. Although clinical trials require substantial amounts of funds, it is essential that they be conducted because of the importance of questions that need to be addressed clinically in order to improve the health of the American people. A combination of basic and clinical research, including clinical trials, is desirable.

We estimate that the new NIDDM prevention trial, which is beginning its full-scale phase in 1994, will last approximately seven years and will cost a total of approximately $100 million.

HEMATOLOGY CENTERS

Mr. Smith. You have three hematology research centers that will move from the planning to operations stage in 1994. What is your long-term plan for this type of center?

Dr. Gorden. Seven exploratory grants were funded in FY 1993 for the planning of Centers of Excellence in Molecular Hematology. In FY 1994, the Institute plans to fund up to three full-scale centers.

The long-term goals for these centers are fourfold: to create a focus for multidisciplinary investigations into the cellular and molecular basis of genetic diseases of the blood; to encourage the efficient assembly of needed expertise, equipment, and technologies to generate advances in molecular hematology; to attract new scientific expertise into the study of the molecular mechanisms of hematologic diseases and disorders; and to utilize cellular and molecular biology techniques to develop methods to characterize, identify, treat, and cure inherited diseases of the blood and genetic diseases of other systems. The Institute has also launched an initiative to stimulate individual research grant applications in the area of stem cell biology, as a complementary means of expanding fundamental hematologic research.

DISEASE RESEARCH SUPPORT

Mr. Smith. Please provide estimated 1993-1995 funding for the following: diabetes, interstitial cystitis, obesity, prostate, inflammatory bowel disease, celiac disease, osteoporosis, nutrition, cystic fibrosis, polycystic kidney disease, Cooley's anemia, sickle cell anemia, IgA nephropathy, and Crohn's disease.

Dr. Gorden. Our support for those areas is as follows:

NIDDK Support for Selected Disease Areas
(dollars in thousands)

	1993 Actual	1994 Estimate	1995 Request
Diabetes and Related Research	187,100	196,800	204,100
Interstitial Cystitis	7,991	8,400	8,700
Obesity	31,600	33,200	34,500
Prostate	9,790	10,300	10,700
Inflammatory Bowel Disease	11,500	14,000	14,500
Celiac Disease	1,884	2,000	2,100
Osteoporosis	17,379	18,300	19,000
Nutrition	78,600	82,700	85,700
Cystic Fibrosis	21,676	23,200	24,100
Polycystic Kidney Disease	5,079	5,300	5,500
Cooley's Anemia	5,005	5,300	5,500
Sickle Cell Anemia	6,142	6,500	6,700
IgA Nephropathy (Glomerulonephritis)	11,954	12,600	13,000
Crohn's Disease (Inflammatory Bowel Dis.)	11,500	14,000	14,500

RESEARCH CENTERS

Mr. Smith. Identify the number, type and subject matter of research centers supported in 1994.

Dr. Gorden. The NIDDK will support 58 research centers in 1994. They span most of our research programs, and range in age from our Diabetes Research and Training Centers, which have been in existence as a program for over 20 years to our Molecular Hematology Centers, which are new in 1994.

Research Center Programs of the NIDDK

Diabetes-Endocrinology Research Centers	6
Diabetes Research and Training Centers	6
Digestive Diseases Research Centers	12
Cystic Fibrosis Centers	5
Gene Therapy Centers	3
Obesity\Nutrition Research Centers	4
Clinical Nutrition Research Centers	5
George M. O'Brien Kidney and Urological Research Centers (Kidney)	7
George M. O'Brien Kidney and Urological Research Centers (Urology)	5

Research Centers of Excellence in Pediatric Nephrology and Urology	2
Centers of Excellence in Molecular Hematology	3
Total in 1994	58

POLYCYSTIC KIDNEY DISEASE

Mr. Smith. We hear that important progress is being made by some of your researchers working on matters related to Polycystic Kidney Disease. Would you tell us about this?

Dr. Gorden. Let me give you two examples of recently reported, NIDDK-supported basic research that suggest the possibility of eventual treatments to prevent or delay the cyst enlargement in polycystic kidney disease (PKD) that destroys kidney function. In one study, investigators studied cysts removed from PKD patients with end-stage renal disease. They found that the cysts could secrete fluid. They also found that the secretion could be altered by added substances and by as yet unidentified substances in the cyst fluid. The finding that cysts may absorb as well as secrete fluid led the researchers to conclude that drugs might be developed to alter net secretion of fluid from cysts and thereby inhibit cyst enlargement.

In another study, investigators developed an in vitro model of spontaneous cyst formation and determined that certain substances could inhibit cyst formation in the test tube. They then tested those substances in a mouse strain that develops PKD and dies from uremia by four to five weeks of age. They found that mice treated weekly with taxol survived more than 200 days with minimal loss of kidney function. Their results suggested that taxol may be useful in treating PKD in humans.

Both of these studies are very preliminary in terms of their clinical application. However, we are encouraged greatly by their implications.

Mr. Smith. Approximately how many researchers are working under NIDDK grants on PKD? and how much money is allocated this year to this disease?

Dr. Gorden. In fiscal year 1993, the NIDDK expended $5.1 million for PKD research. Those funds supported approximately 30 grantees. In fiscal year 1994, we estimate that PKD research funding will be approximately $5.3 million.

Mr. Smith. In recent years, NIDDK has funded a number of interdisciplinary centers under various names. Would it not be a good idea to utilize this approach for PKD?

Dr. Gorden. The current Kidney, Urology, and Hematology Centers program is anchored in very broad areas: the George M. O'Brien Kidney and Urological Research Centers, Research Centers of Excellence in Pediatric Nephrology, and Centers of Excellence in Molecular Hematology. This allows the wide competition necessary to ensure that the Centers that are established focus on those topics most likely to benefit from the Centers mechanism. PKD researchers can compete for George O'Brien and Pediatric Nephrology Center awards. However, until the science base for PKD becomes larger, I believe that individual investigator-initiated research grants are more likely to increase understanding of the disease and generate new research leads.

TRANSPLANTATION RESEARCH

Mr. Smith. Are you providing support for the scientists who need human adult pancreas and fetal pancreas for islet cell transplant research, as mandated by the Diabetes Control and Complications Trial?

Dr. Gorden. The support of research resources such as human fetal tissue is accomplished through components of the NIH other than the NIDDK. With regard to the Diabetes Control and Complications Trial, it investigated the effect of intensive treatment for insulin-dependent diabetes on the onset and progression of long-term health complications of this disease. In this trial, diabetic patients either were on standard or intensive regimens of liquid insulin administration. Cell or tissue transplantation was not a part of the study.

GENETICS OF DIABETES

Mr. Porter. Dr. Gorden, can you please give me an update on the genetics of diabetes? What are you doing to find the genes that play a role in causing diabetes?

Dr. Gorden. Genetics appears to be the common denominator underlying the various factors that are involved in the development of diabetes. The identification of specific genes involved in diabetes represents a major goal of biomedical research. The NIDDK recognizes this area as a high priority for research and has taken steps to encourage research in the genetics and molecular biology of diabetes. Recently, human genetic analyses based on either population studies or pedigree analyses have confirmed the association between specific gene constituents and insulin-dependent diabetes mellitus (IDDM). The results also suggest that certain constituents primarily confer protection from disease to an individual who is a member of a high-risk population for IDDM while certain other constituents confer susceptibility to disease. Identification of genetic variants that predispose to or protect from IDDM are extremely useful. Combining genetic screening with immunological marker analyses will strengthen our ability to recognize individuals at high risk for the development IDDM. This will be especially important as we progress into the screening of specific populations to find at-risk individuals who are not first-degree relatives of IDDM patients.

In other genetic studies of families with maturity-onset diabetes of the young (MODY), which is a form of non-insulin-dependent diabetes mellitus (NIDDM), a very close association was demonstrated between the gene that produces a critical enzyme for glucose metabolism and disease status. These results imply that mutations in this gene may be the cause of diabetes in MODY families. In fact, subsequent studies revealed mutations in 18 of 32 MODY families; the mutations were not found in typical NIDDM (non-MODY) families. In related research, NIDDK grantees localized this gene mutation to a specific chromosome. This marks the first time that a genetic mutation in a key enzyme for glucose metabolism has been shown to cause diabetes.

These are but two examples of the rapid progress that is being made in genetic studies of diabetes. Intensified genetics research offers great promise for understanding, controlling, and preventing diabetes. The NIDDK will continue to enhance support for both the basic understanding of diabetes and for the direct application of this knowledge to improve the health of diabetics.

UROLOGIC DISEASES OF WOMEN

Mr. Porter. I understand that your Institute recently sponsored a conference on urologic diseases of women and that you have also issued a research solicitation to encourage additional grants in this area. Scientifically, how do you see this area developing?

Dr. Gorden. Over the past years, the NIDDK has made a strong effort to increase meritorious research in the area of women's urologic health. In FY 1993, the Institute announced two program initiatives: one on interstitial cystitis (IC) and other bladder disorders of women, and one on innovative approaches to the study of IC. In FY 1994, the initiative on IC and other bladder disorders of women was announced again, with the anticipation that 10 to 15 additional awards will be made in the areas of urinary tract infection, urinary incontinence, and IC. The NIDDK also supports an IC patient data base, with the objective of providing new insights and research leads related to IC.

In March 1994, the Institute sponsored a three-day "Symposium on Women's Urological Health." This symposium brought together speakers and participants from various research disciplines (including microbiology and infectious diseases, neurology, gynecology, pharmacology, surgery, physiology, epidemiology, and geriatric medicine) to focus on the problems of urinary tract infection, urinary incontinence, and IC. This opportunity for forging interdisciplinary collaborations was applauded by the participants and is likely to lead to new research approaches.

ONSET OF DIABETES

Mr. Porter. What major research efforts is NIDDK making to prevent the onset of diabetes?

Dr. Gorden. Building on the results of the recently-completed and very successful Diabetes Control and Complications Trial, the NIDDK has begun a new and comprehensive initiative to prevent diabetes and its complications. This multi-faceted initiative encompasses basic and applied research, clinical studies and trials, and national multicenter trials supported by the NIDDK. One trial recently begun is the Insulin-Dependent Diabetes Mellitus (IDDM) Prevention Trial, which is studying the primary prevention of IDDM in intermediate and high-risk first-degree relatives of individuals with IDDM. Several molecular markers have been discovered which can be used to identify individuals at very high risk for IDDM. Encouraging pre-trial data suggested that modifying the pre-diabetics' immune system may be effective in preventing IDDM. This major clinical trial will test vaccine-like interventions in prediabetic individuals, using injected or oral insulin, to attempt to prevent or delay the onset of IDDM.

POLYCYSTIC KIDNEY DISEASE

Mr. Porter. How much money is allocated by NIDDK to research focused on PKD as compared with other genetic diseases such as cystic fibrosis? Since PKD affects many more people than the other chronic genetic diseases, and since the Federal government pays most of the cost of dialysis and transplants for PKD patients, wouldn't it be a good investment to lift PKD research up with these other areas of research?

Dr. Gorden. The FY 1994 NIDDK funding estimate for cystic fibrosis (CF) research is $23.2 million, or approximately fourfold that for PKD. Though we have not calculated the exact funding figures for other inherited diseases, we estimate them to be less than, or similar to, the figure for PKD. Factors affecting funding decisions include the state of scientific knowledge about a disease, research leads and opportunities emerging from that scientific base, and the cadre of trained investigators to follow those leads. The seriousness of the disease and its impact on the Nation are also considered, as well as the need to maintain a balance among our research programs and mechanisms.

Funding for CF virtually exploded after the gene that is defective in approximately 70 percent of cases was identified and cloned in 1989. At the same time, a large amount of knowledge had accumulated about the mechanisms of the disease, and a large pool of excellent investigators had developed a firm foundation in CF research. The Institute, with advice from the community, concluded that the time was right for an accelerated effort in CF research, including the funding of gene therapy centers, with an emphasis on CF, which received special funding from the Congress. It is hoped that what is learned at these centers will also have relevance to other genetic diseases such as PKD.

ORGAN TRANSPLANTATION

Mr. Stokes. The NIH investment in organ transplantation has grown significantly over the years, yet I remain concerned that African Americans and other minorities have not fully benefitted from this life saving research. African Americans are about 42 percent of the over 32,000 individuals on the waiting list, and there is the problem of transplant rejection. Doctor, what specifically is your institute doing to increase the benefits of organ and tissue transplantation research to African Americans and other minorities? What is the extent of your Institute's investment in this area?

Dr. Gorden. The NIDDK supports research on kidney, liver, pancreas, and bone marrow transplantation. NIDDK funding for organ transplantation research is estimated to be approximately $25 million in FY 1993 and $26 million in FY 1994. Let me tell you briefly about our programs in kidney and liver transplantation.

The NIDDK encourages research to understand kidney-immune system interactions at the molecular level, research to seek sensitive methods of measuring graft rejection, and research on methods for suppression of rejection by manipulation of cytokines (hormone-like substances) that affect immune response or kidney function. Initially, graft rejection seems to be immunologic, with the recipient rejecting an organ that is not an exact immunologic match to his or her own tissue. However, this initial period is followed by a longer period during which rejection is largely a consequence of declining kidney function. NIDDK-supported basic research on kidney function is therefore directly relevant to the success of transplantation. An example of such research that focuses specifically on African Americans is the basic research supported by the NIDDK on genetic and cellular mechanisms of kidney disease associated with hypertension in African Americans.

In the area of liver transplantation, the Institute is currently supporting studies to perfect an artificial liver that will tide a patient over until his own liver recovers or until a suitable donor can be located. Though liver transplants are life saving, they are costly, and it is often difficult to locate appropriate livers in an emergency. Encouraging clinical observations also have been made involving the migration of cells from the transplanted organ to the organ recipient, which suggests the possibility of induced tolerance to transplanted organs. Induced tolerance would both improve the patient's quality of life and reduce the cost of transplantation. To further promote liver disease research, the NIDDK supports a liver transplantation data base which gathers data for evaluation from patients undergoing liver transplantation and provides ready access of such data to investigators and clinicians. A liver tissue procurement and distribution system provides investigators with normal and diseased liver tissue for research.

MOLECULAR BIOLOGY

Mr. Stokes. Can you highlight for us what advances could stem from increased investments in molecular biology, as it relates to the diseases and disorders under the purview of your institute?

Dr. Gorden. The techniques of molecular biology and recent advances in knowledge made possible by those techniques have led to a revolution in medical science and to innovative clinical approaches to disease. The NIDDK has been a participant in this revolution. With NIDDK support, many critical genes have been identified, including: genes encoding insulin, erythropoietin, human growth hormone; genes encoding various hormone receptors; genes underlying such metabolic diseases as cystic fibrosis, Tay-Sachs disease, and Fabry's disease; and candidate genes that may be involved in diabetes and obesity. The cloning of such genes is important as a tool for further research in understanding diseases and as a basis for the development of methods to predict, diagnose, and treat them. For example, ongoing initiatives in gene therapy for cystic fibrosis and prevention of insulin-dependent diabetes are made possible by basic molecular biology research. Further, molecular biology research has a direct relationship to important advances in biotechnology, such as recombinant DNA, development of transgenic animal models for human disease, diagnostic tests based on PCR (the polymerase chain reaction), and development of biologic interventions to manipulate gene expression.

Identification of molecular mechanisms involved in diabetes, obesity, and kidney failure remains a major goal of NIDDK-supported research. In addition, the NIDDK plans to establish, this year, three Centers of Excellence in Molecular Hematology to create a focus for multidisciplinary investigations into the cellular and molecular basis of genetic diseases of the blood. We believe that this investment in molecular hematology research will also have implications for other, non-hematologic, diseases. The NIDDK has identified many other areas of opportunity in molecular research, which the Institute hopes to support or continue to support in the years to come. These include:

new methods of gene therapy for genetic metabolic diseases; mechanism of action of estrogen in bone; key regulatory steps in endocrine control of cell growth involved in breast disease; molecular mechanisms of inflammatory bowel disease; and increased research on hematopoietic stem cell biology and gene regulation. We believe that advances in these areas could lead to better diagnosis and treatment of the many diseases within the Institute's purview.

GENE THERAPY

Mr. Stokes. Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offering the most hope through further advances and investments in gene therapy. Elaborate briefly. How much is included in the FY 1995 budget request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Gorden. This year there have been major steps forward in our efforts to move gene therapy from the laboratory to the bedside. Presently, human gene therapy trials are being conducted for two genetic diseases -- hypercholesterolemia and cystic fibrosis -- and protocols have been approved by the NIH Recombinant DNA Advisory Committee (RAC) for Phase I studies for the treatment of Gaucher's disease. In addition, one of the major areas of hematology research involves the development of specialized cells that can be used in gene therapy for genetic diseases. I would like to elaborate on two of these examples.

The NIDDK is contributing support to the human study of gene therapy for familial hypercholesterolemia. In this study conducted at the Gene Therapy Center at the University of Pennsylvania, researchers remove a portion of the patient's liver, isolate liver cells, insert a gene that produces the low-density lipoprotein receptor, and inject the genetically altered cells into the patient's liver where the cells colonize the liver and begin producing the protein that is critical to preventing the unwanted build-up of cholesterol. Unlike previous gene therapy protocols, insertion of this gene should be permanent. In the first treated patient, researchers recently reported that gene expression has persisted for nearly two years and lowered cholesterol levels by 20 percent. Administration of a lipid-lowering drug reduced cholesterol levels an additional ten percent. Thus, the researchers are demonstrating the safety and effectiveness of gene therapy in this patient.

The RAC has approved seven human Phase I trials for cystic fibrosis, and three are currently underway. Many of the protocols were developed with support from an NIDDK initiative in FY 1992 entitled "New Therapies for the Treatment and Cure of Cystic Fibrosis." Most of these protocols use an adenoviral vector to deliver the corrected cystic fibrosis transmembrane regulator (CFTR) gene. One such study is being conducted at the Gene Therapy Center at the University of Pennsylvania. Another of the approved protocols that obtained its preclinical data with support from the NIDDK is the first to propose the use of liposomes to deliver the CFTR gene. In addition, research is underway at several universities based on studies originally initiated in the NIDDK intramural program to develop adeno-associated virus as a vector for delivery of CFTR to the lung.

These diseases represent only a fraction of the possible diseases treatable by gene therapy. Future targets for gene therapy include genetic hematologic, metabolic, kidney, and liver diseases, as well as disorders such as diabetes. In order to extend the repertoire of diseases that can be treated by gene therapy, the NIDDK supports basic research in identification and characterization of genetic diseases; localization of disease-causing genes; development of vectors and gene delivery systems; and the identification and isolation of appropriate stem cell targets for gene therapy. Recently, investigators have brought two genetic kidney diseases closer to the possibility of gene therapy. The gene and mutations responsible for Alport syndrome, an inherited disorder that can lead to kidney failure and deafness, have been identified and cloned. Investigators have also mapped the gene for polycystic kidney disease.

In summary, the NIDDK continues to support and foster research related to gene therapy in a variety of ways. The Institute looks forward to the contributions of the many investigators it supports to the development of modern methods of treating and curing disease. The NIDDK's support of gene therapy research was approximately $35 million in FY 1993 and is estimated to be approximately $37 million in FY 1994.

EMPHASIS IN MINORITY HEALTH

Mr. Stokes. With regard to diseases and disorders that affect minorities, what are the most significant areas of research that are supported and conducted by your institute?

Dr. Gorden. The most significant areas of research in the NIDDK with regard to diseases and disorders that disproportionately affect minorities are diabetes, obesity, gallstones, kidney disease, and sickle cell anemia. However, minority and non-minority groups alike derive health benefits from all research supported and conducted by the NIDDK.

Mr. Stokes. As the Director of an institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues -- while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure diseases, and, while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Gorden. The magnitude of the public health problem affecting minority populations impacts on total health care costs of the Nation. Research advances in the basic biomedical sciences ultimately find application in the clinical setting. Ideally, treatments for disease are available to all Americans. The matter of accessibility is another issue. We, at the NIDDK, and at the NIH in general, would wish that all people could benefit equally from this Nation's investment in research.

RESEARCH TRAINING

Mr. Stokes. For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your institute?

Dr. Gorden. To maintain an adequate pipeline of investigators in biomedical science, two basic elements are necessary. First, individuals must have the interest to pursue a career in research, and, today, incentives to do research often play a significant role in that. And secondly, research training really is contingent upon available resources. The NIDDK very carefully manages its training resources and continually re-examines and plans ways in which research training opportunities may be enhanced.

To increase participation of minorities in research training and research careers, the NIDDK has dedicated training positions for physicians and basic scientists from underrepresented minority groups through National Research Service Awards (NRSA). These awards provide research training under the guidance of nationally recognized researchers so that they may compete for NIH grant support and fill leadership roles in the biomedical sciences and academic medicine. In addition, underrepresented minorities are supported through the NIDDK small grants program (R03). This program enables recently trained M.D. and/or Ph.D. minority investigators to gain additional research experience and to obtain data on which to base a subsequent R29 or R01 research grant application.

CLINICAL RESEARCH

Mr. Stokes. What are some of the most exciting and most promising clinical research opportunities at your Institute? Elaborate on the benefits to be achieved from further investments in this research.

Dr. Gorden. The NIDDK has prepared plans for many clinical trials that we believe would contribute substantially to the improve health of the American people. These trials include, but are not limited to the following: immunosuppressants in Crohn's disease, a form of inflammatory bowel disease; treatment and prevention of recurrent bleeding of ulcers by eradication of Helicobacter pylori; prevention and treatment of kidney disease of diabetes; and several other trials related to diabetes, and digestive and kidney diseases. The impact of scientific advances resulting from these trials -- the prevention and successful treatment of disease -- on improvements in quality of life and reductions in morbidity and premature mortality would yield significant health care cost savings and benefit the American public.

MINORITY RESEARCH AND RESEARCH TRAINING

Mr. Stokes. Please describe the measures your institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported.

Dr. Gorden. When planning program initiatives, the NIDDK always pays particular attention to including representation of minority groups and women as appropriate. Research investigators from many disciplines, including basic scientists, clinicians, and epidemiologists, assemble at conferences and workshops at least once per year to make recommendations to the NIDDK on diseases that disproportionately affect minority populations. The NIDDK has reserved National Research Service Awards training positions to provide research training opportunities to underrepresented minority trainees with particular attention to encouraging the development of minority scientists and clinicians who will pursue research careers. Minority researchers receive research training to prepare them to compete favorably for independent NIH grant support and to fill leadership roles in the biomedical sciences and academic medicine.

Mr. Stokes. What significant initiatives in minority health research and research training, and outreach are supported by your institute?

Dr. Gorden. I am pleased to provide some examples of initiatives that target minority populations. In diabetes, the NIDDK is supporting a clinical trial program on the treatment and prevention of non-insulin-dependent diabetes mellitus (NIDDM) and its complications, which disproportionately affect minorities. This trial is targeted at individuals with impaired glucose tolerance, a history of gestational diabetes, and/or newly diagnosed NIDDM. Interventions may include diet, exercise, and pharmacologic agents. Minorities will make up 50 percent of the study population. The NIDDK continues support of obesity research through its regular research program, through increased obesity research within the Clinical Nutrition Research Units (CNRU) program, and our Obesity and Obesity/Nutrition Research Centers (ONRC). Another clinical trial on new approaches to weight control in minority populations has begun. This multicenter clinical trial is a culturally sensitive weight control program for African-American women. In addition, the Institute has created a National Task Force on Prevention and Treatment of Obesity as a subcommittee of the National Digestive Diseases Advisory Board to help synthesize current scientific information about various aspects of obesity and weight loss and to identify concepts for possible future clinical studies concerning obesity. In the past year, the Task Force sponsored and co-sponsored workshops and conferences. As a result, the Task Force is developing a long-range obesity research agenda to examine the current opportunities in basic and clinical research relating to obesity and assess for future research directions, particularly in the clinical area. In the area of kidney diseases, the NIDDK is expanding studies on the development of kidney disease and hypertension, and progression to end-stage renal disease in African Americans. Also, the NIDDK is funding a multicenter study examining the impact of three antihypertensive drug regimens with different initial randomized drugs and two different levels of blood pressure control on kidney function in African American subjects with hypertension and established kidney disease. The study of diabetic renal disease in the Pima Indian population to increase our knowledge of diseases in the Native American population supports a clinical trial addressing the deleterious effect of hypertension and altered kidney function as mechanisms leading to kidney injury in NIDDM.

The NIDDK training and outreach programs continue to receive high priority in our efforts to reach minority populations and communicate effectively about diseases that disproportionately affect these groups. The NIDDK-supported Diabetes Research and Training Centers (DRTC) training and translation program supports studies to translate advances in the field of diabetes research into improved care for the diabetic. The application of this focus to diabetes in minority populations has been reinforced in a statement in the revised DRTC guidelines that state "the NIDDK is concerned with disproportionate prevalence of diabetes in minority groups and the increased susceptibility to the complications of diabetes in these groups." Also, the NIDDK has issued a solicitation for FY 1994 funding which will establish an Obesity Research Information Center to enhance the transfer and translation of research findings concerning obesity and nutrition to clinical applications and public awareness through the development of strategies of communication focused on prevention as well as treatment programs.

The NIDDK diabetes outreach efforts include the National Diabetes Information Clearinghouse develops and disseminate information to the public in the diabetes field, and responds to about 15,000 requests for information per year. The audience includes professionals, including nurses, dietitians, diabetes educators, and physicians. Because of the self-care nature of diabetes, a large number of users are patients and their families. Also, the National Digestive Diseases Information Clearinghouse responds to about 10,000 inquiries per year to enhance the knowledge and understanding of digestive diseases. In addition, the National Kidney and Urologic Diseases Information Clearinghouse collects information about lay-oriented education materials in the kidney and urology fields, and distributes 60,000 publications per year.

To enhance our research training efforts, the NIDDK requires that principal investigators on all NRSA training grants propose and implement a plan to identify and recruit minorities into his or her research training program and fill training positions that have been dedicated for this purpose. In addition, the NIDDK continues to support underrepresented minority investigators on administrative supplements of NIDDK-supported grants to further increase the number of minorities in biomedical research.

Mr. Stokes. How does your institute identify its priorities for investments in minority research and research training?

Dr. Gorden. The NIDDK receives recommendations from many sources, including our community of research investigators, our National Advisory Council, our three National Advisory Boards along with other advisory groups, the U.S. Congress, the Public Health Services' report Healthy People 2000: National Health Promotion and Disease Prevention Objectives, the Office of the Secretary of DHHS, voluntary and professional organizations, and focussed scientific workshops and other conferences.

Mr. Stokes. When the Office of Research on Minority Health provides funds to your institute, do these funds typically augment existing minority programs or efforts, or do they replace funds your institute previously invested in its minority research and research training initiatives, elaborate.

Dr. Gorden. I am particularly pleased to be able to discuss the productive partnership we have formed with the Office of Research on Minority Health (ORMH). Over the past three years, ORMH has provided substantive support to the NIDDK that has allowed us to add activities to our research portfolio that we would otherwise have been unable to undertake. For instance, the ORMH is providing half of the funds for two clinical studies that fell just outside the NIDDK payline and would have been unfunded. Based on the ORMH commitment, NIDDK has provided the remainder, in an excellent example of the type of leverage that ORMH can foster. These two studies are an investigation of "Pathogenesis of NIDDM in Mexican American Women," and a trial of "Long-Term Outcome of Obesity Treatment in Minority Women." Of particular importance has been the ORMH plan to continue contributing support for these trials for the full award period.

In addition, ORMH is supporting the addition of an important component to the upcoming NIDDK trial on primary prevention of NIDDM. This component is an arm of the trial enrolling obese minority women with gestational diabetes-- a group at very high risk for developing NIDDM. The three-year commitment of funds by ORMH to this component allowed us to plan efficiently for the trial, announcing the ORMH interest in and support for the gestational diabetes arm in the solicitation for the trial. It is my belief that this is a model collaboration that will prove to be a very important contribution to minority health.

ORMH funds have also allowed us to support an additional minority medical institution, King-Drew Medical Center, as a center in the pilot phase of the African-American study of Kidney Disease and Hypertension. ORMH also has contributed to fund a study of recruitment of African-Americans in conjunction with the trial.

In FY 1994, the ORMH will be providing funds to enable us to start up studies of the genetics of diabetes in minorities. In FY 1995 and 1996, the ORMH intends to provide ongoing support for nine studies of diabetes intervention in minority populations. Finally, ORMH has provided supplemental support to a range of existing NIDDK grants for activities such as basic research on sickle cell anemia, international meetings on obesity prevention, and investigation of gallstones in Native Americans.

Overall, ORMH support has been used to facilitate NIDDK activities that could not have been funded without this extra help. NIDDK also has contributed a major share to the joint activities, making them a true collaboration in every sense.

Mr. Stokes. When your Institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health? To what extent is there a collaborative relationship between the two organizations, elaborate.

Dr. Gorden. The NIDDK and the ORMH have evolved a cooperative and collegial relationship that has resulted in a number of joint minority initiatives reflecting the priorities of both organizations. Let me explain how we have worked together to focus on the most appropriate areas for collaboration. Initially, I met with Dr. Ruffin, the Director of ORMH, to discuss his general concepts for initiatives to improve minority health. After this discussion, the NIDDK developed some suggestions for joint activities that addressed both the ORMH's interests and the NIDDK's priorities. I have been very pleased with the ORMH response to our ideas. As I've mentioned, the result of follow-up discussions with ORMH has been the joint evolution of a number of specific collaborations that reflect the priorities of both organizations.

CLINICAL TRIALS

Mr. Stokes. How much is included in the FY 1995 budget request for clinical trials? How does this amount compare with the amount invested in clinical trials in FY 1994 and FY 1993? Would you please comment on the economic benefits and the quality of life benefits of some of the major clinical trials supported by your institute?

Dr. Gorden. The 1995 budget request includes an estimated $43.3 million for major clinical trials. This compares with an estimated total of $44.2 million in FY 1994 and an actual total of $31.7 million in FY 1993.

Clinical trials are really the ultimate test of therapies derived from the fruits of basic research. Trials that establish a standard mode of therapy can reduce health care costs and improve quality of life. The cost to the Nation of diseases studied under the purview of the NIDDK is about $300 billion each year; the cost of diabetes alone is estimated to be nearly $92 billion. We are conducting several major trials at this moment. These are trials for preventing both insulin and non-insulin-dependent diabetes, and a trial of kidney disease and hypertension in African Americans to name three. Potentially significant human and economic benefit will come with their completion. By way of example, the Institute's 10-year Diabetes Control and Complications Trial (DCCT) which finished last summer produced impressive results and recommendations. Many billions of dollars and enormous human suffering could be saved from the implementation of the DCCT's recommendations.

Mr. Stokes. To what extent has the institute increased the number of minorities participating in it clinical trials, what progress is being made?

Dr. Gorden. The NIDDK has increased the number of minorities participating in clinical trials through the support of new studies in diabetes, obesity, and end-stage renal diseases, involving large numbers of minorities. In diabetes, the NIDDK has begun a multifaceted initiative aimed at preventing diabetes and its complications encompassing basic and applied research, clinical studies and trials, and national multicenter trials, including a non-insulin-dependent diabetes mellitus (NIDDM) Prevention Trial. The NIDDM Prevention Trial of intervention strategies is targeted at people with impaired glucose tolerance (IGT) and a history of gestational diabetes and/or newly diagnosed NIDDM. Minority subjects will make up 50 percent of the study population. In obesity, the Institute is supporting a clinical trial to study new approaches to weight control in minority populations. This trial is a culturally sensitive weight control program for African American women. The program can be administered through church and community centers by trained African American lay persons. In addition, NIDDK currently supports research on gallbladder ultrasonography in the third National Health and Nutrition Examination survey. Researchers are investigating ultrasonography of the gallbladder among approximately 4,000 adult indians to determine the prevalence of gallstones, and correlate it with the multiple risk factors data collected in the survey. In kidney diseases, the NIDDK is funding a multi-center study on African American subjects with hypertension and established renal disease. Recruitment for this clinical trial program has been accelerated by the participation of

Howard University, Martin Luther King-Drew Medical Center, Meharry School of Medicine and Morehouse School of Medicine.

Mr. Stokes. I understand that a number of the institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place: Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Gorden. This mechanism has been supported by the NIDDK since 1989. Since inception of this mechanism, the NIDDK has supported more than 200 minority researchers. Two percent of this number have successfully competed for independent research project grants. The program is still too new to show a large measure of success but it provides an excellent opportunity for minority researchers to participate in high quality research projects.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes. What are some of the major initiatives underway at your institute to increase the participation of Historically Black Colleges and Universities in biomedical research?

Dr. Gorden. The NIDDK Minority Travel Award helps to broaden the research interest of minority investigators and provides a forum for discussing the focus of their investigations. This funding supports the travel of undergraduate, predoctoral, and postdoctoral minority students and full-time faculty members from minority institutions to national scientific meetings. The goal is to facilitate minority investigator interaction with scientists who have similar scientific interests. The NIDDK continues to seek and invite recommendations from community organizations, investigators, and advisory groups concerning additional ways for increasing the participation of Historically Black Colleges and Universities in biomedical research.

PERSONNEL

Mr. Stokes. How many GS-15 and above positions are there in your institute? How many employees in your institute are in GS-15 and above positions? In your institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem in your institute?

Dr. Gorden. There are 99 GS-15 or equivalent and above positions which includes Commissioned Officers, in the NIDDK. Currently, all 99 positions are filled. We have four African Americans at the GS-15 or equivalent level. All four are Medical Officers in the Public Health Services Commissioned Officers Corp. Two are CO-5s and two are CO-6s. There are no cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level. NIH has discussed relief from the freeze with the Assistant Secretary for Health on several occasions, but as of this date, the NIH has not received any relief from the current hiring and promotion freeze. If the restrictions were to be lifted, however, the NIDDK would continue to pursue the diversification of the work force and would actively seek to promote African Americans to the GS-15 and above level.

DISEASE PREVENTION

Mr. Stokes. With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Gorden. Prevention research spans the breadth of NIDDK-supported basic and clinical investigations, and the Institute has initiated a number of very promising programs aimed at disease prevention. These initiatives include major clinical trials on the primary prevention of insulin- and non-insulin-dependent diabetes mellitus, kidney disease and hypertension in African Americans, which I have already mentioned.

Other prevention research under way includes studies on the use of combination drug therapy, which effectively eradicates the bacterium associated with peptic ulcer disease and reduces the rate of ulcer recurrence; a clinical trial to investigate if early therapy with a beta-adrenergic blocker can prevent or delay the development of gastroesophageal varices; and research to test whether a weight-control intervention for middle-aged African American women will affect the risk factors for disease.

Nutritional disorders contribute to a wide range of chronic and debilitating conditions. In recognition of the potential importance of nutrition in prevention, NIDDK is taking the lead in developing a trans-NIH Bionutrition Initiative in an area of fundamental nutrition research that is of importance to many of the NIH institutes. In addition, the Institute has an ongoing Obesity Initiative, aimed at enhancing obesity prevention and treatment research and at the communication of this research to the public. This spring, the Institute will formally initiate an Obesity Resource Information Center to serve as an information resource to the public and to health care providers, and to develop pilot education projects for minorities and at-risk populations. The NIDDK-sponsored National Task Force on Prevention and Treatment of Obesity has recently reviewed obesity research opportunities and now is finalizing its report, which includes specific recommendations for obesity prevention research.

Additional studies supported by our kidney and urology programs include the prevention of morbidity and mortality in hemodialysis patients, and the use of drug therapy to prevent the progression of benign prostatic hyperplasia.

All of these studies, of course, are predicated on many years of successful support of basic research.

BIOTECHNOLOGY

Mr. Stokes. Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your institute.

Dr. Gorden. Increased research in biotechnology is vital because it is a key point at which knowledge from basic research produces practical new tools for continuing innovative research and for diagnosing and treating disease.

For example, NIDDK-supported basic research contributed to the development of recombinant techniques to produce large quantities of erythropoietin, growth hormone, and insulin -- all now used for treating disease. This year, NIDDK researchers are participating in Phase III clinical trials of recombinant human thyroid-stimulating hormone for the diagnosis of residual cancer cells in patients being treated for thyroid cancer. These trials are a direct result of years of molecular research at the NIDDK, during which researchers cloned the gene for thyroid-stimulating hormone, developed methods to produce it in animals, and ascertained its clinical application.

NIDDK grantees and researchers are involved in developing transgenic animals for the study of disease and for the production of therapeutic proteins. Investigators have used transgenic technology to create lines of transgenic mice that have a primary deficiency of brown adipose tissue and have found that the mice with reduced amounts of this tissue, commonly called "brown fat," have severe obesity. Their study suggested an important role for "brown fat" in obesity.

Intramural investigators have recently reported the development of a "Tay-Sachs" mouse, which will provide an important research tool for increased understanding of, and development of genetic treatments for, this disease.

Work continues with industry in developing methods of producing human therapeutic proteins -- such as anti-clotting proteins and clotting factors -- in the milk of farm animals, with the hope of reducing the cost of producing such proteins for medical use.

NIDDK scientists have developed a method of diagnosing the thalassemias and are working on biologic methods of introducing healthy genes into a person's DNA or introducing missing enzymes into the bodies of patients in a form that does not disintegrate before the enzymes can work.

This year, Institute grantees reported progress in the use of recombinant adenovirus to introduce healthy genes into pancreatic cells. Adeno-associated virus continues to be studied as a vehicle for gene therapy in cystic fibrosis and AIDS.

NIDDK intramural investigators identified "gene insulators" in DNA, a discovery that could lead to improved human gene therapy techniques, whereby the genetic material to be inserted into a patient's DNA could be protected from the possibility of inappropriate regulation. Other investigators are working on biologic techniques involving monoclonal antibodies, ribozymes, or antisense technology with the goal of disabling the human immunodeficiency virus.

I hope that these examples communicate the importance of biotechnology in moving biomedical research forward.

MINORITY INSTITUTIONS

Mr. Stokes. What is the present level of support provided to minority institutions by your institute?

Dr. Gorden. In FY 1993 the NIDDK awarded $689 thousand to Historically Black Colleges and Universities. We estimate that the level of support in FY 1994 will be approximately $760 thousand and in FY 1995 approximately $835 thousand.

Mr. Stokes. Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the institute's programs and activities?

Dr. Gorden. The NIDDK has met with the DHHS Task Force on Blacks and Minority Health and representatives from historically black colleges and universities with a view toward developing new initiatives that could be tailored for participation from these groups. Until a stronger mechanism is developed to enhance research capabilities at Historically Black Colleges and Universities, the NIDDK will maximize its use of the Administrative Supplement through which minority investigators at minority institutions may collaborate on research with NIDDK-funded investigators. Also, science teachers may receive laboratory research experience through the NIDDK-supported American Physiological Society Program to enhance their experience in physiology. In addition, secondary school science teachers and students from the District of Columbia may participate in biology research laboratories at the Catholic University of America to encourage minorities to choose careers in science, and to improve the quality of science education in District of Columbia schools.

Mr. Stokes. Explain the proposed funding for the programs of your institute designed to increase the participation of underrepresented minorities in biomedical research and research training?

Dr. Gorden. The NIDDK plans to continue supporting underrepresented minority students and investigators studying diseases that disproportionately affect minority population through administrative supplements to NIDDK-supported grants to increase the number of minorities entering and remaining in biomedical research careers. Approximately 110 minority awards are made each year. The NIDDK Honors Undergraduate Research Training (HURT) supports undergraduate and graduate predoctoral scholars to participate in summer research projects in an NIDDK intramural laboratory to broaden his/her research activities by conducting experiments and writing scientific papers. Approximately 30 minority awards are made each year. The NIDDK has reserved training position on National Research Service Awards T32 training grants to ensure the inclusion of minority research trainees.

NATIONAL DIGESTIVE DISEASES ADVISORY BOARD

Ms. Lowey. The Office of Management and Budget has proposed the elimination of the National Digestive Disease Advisory Board. How does the NIDDK view this proposal? In particular, what impact would this have on research and public health education on digestive diseases?

Dr. Gorden. The Administration is seeking to restrain the number and costs of advisory committees in order to stabilize them and conform with the recommendations of the National Performance Review. On February 10, 1993, President Clinton issued an Executive Order calling for the elimination of at least one-third of all advisory committees not required by statute as well as the review of statutorily required committees. We understand that the Administration plans to transmit to the Congress omnibus legislation to terminate statutory committees which are no longer required. It also appears that additional statutory and non-statutory advisory committees have been identified for further in-depth review during fiscal year 1994.

While we recognize the positive contributions made by our disease-oriented advisory boards, it is becoming increasingly difficult to support these types of administrative activities when research funds are limited and our success rate for research project grants is only 22 percent.

HISPANIC HIRING AND PROMOTION

Mr. Serrano. First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Gorden. The NIDDK supports and participates in a number of annual meetings of importance to Hispanics such as meetings of the Society for the Advancement of Chicanos and Native Americans in Science, and annual meetings of the Minority Access to Research Careers and Minority Biomedical Research Support Programs. The NIDDK presence at these meetings enables the institute to publicize research and other opportunities within the Institute. For instance, in October 1993, NIDDK participated in the 8th Annual Symposium of the Hispanic Physicians and Surgeons in San Juan, Puerto Rico. The following week, the Institute met with the same group to discuss research and research training opportunities at the NIH/NIDDK. The Institute also was able to recruit students for the summer intramural research program and Minority Access to Research Careers program.

HISPANIC HEALTH ISSUES

Mr. Serrano. Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Gorden. The NIDDK budget is largely directed toward basic research in cross-cutting areas, such as molecular biology, endocrinology, nutrition, immunology, and genetics, which are widely applicable to all parts of the U.S. population. At the same time, while I cannot give you a precise percentage, I believe that a substantial portion of the NIDDK budget is directed at research that bears on health issues of particular relevance to Hispanics. For example, under the President's Budget submission for FY 1995, we estimate that we will expend the following: $204.1 million on diabetes & related research, $34.5 million on obesity research, and $5.9 million on gallstone research. These diseases have a particularly heavy impact on Hispanic populations. We also believe that much of our kidney disease and related research ($128 million in FY 95) is relevant to Hispanics, who may be overrepresented in the Federal end-stage renal disease program as dialysis and/or kidney transplant patients. We are working with the Health Care Financing Administration's Medicare Program to revise their Medical Evidence Form so that it can report ethnicity as well as race. In this way, we will have better data on the impact of ESRD on Hispanics to guide our research efforts.

In addition to the general areas cited above, the NIDDK has a number of specific studies that target Hispanic populations. Our upcoming major trial on prevention of non-insulin-dependent diabetes (NIDDM) will include the oversampling of Hispanics. We are collaborating with the Office of Research on Minority Health, NIH, (ORMH) to fund a component of the NIDDM trial examining gestational diabetes in obese minority women, a particularly important problem for Hispanic women. Other NIDDK-funded studies cover a wide range of topics, including studies of NIDDM genes in Hispanics, investigations of body composition in a Hispanic population in New York City, and the pathogenesis of NIDDM in Mexican American women (co-funded with ORMH). In addition, as a result of an NIDDK initiative for research on diabetes in minority populations, we will be funding several grants specifically addressing diabetes prevention and treatment in different Hispanic populations. ORMH will be contributing to support of these grants in FY 1995 and 1996. Consistent with NIH policy, when we issue research solicitations for clinical studies, we advise potential applicants of the need for appropriate inclusion of minorities and women in their study populations.

At our Diabetes Research and Training Centers we support studies that help translate health advances to Hispanic populations. For example, researchers are investigating ways to improve the rate of eye exams among Hispanic diabetics and identifying diabetes self-care obstacles experienced in Spanish speaking populations. NIDDK also has contributed to the collection of information concerning Hispanic populations by the National Center for Health Statistics, and has developed information resources in Spanish to assist Hispanics.

HISPANICS IN RESEARCH

Mr. Serrano. Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Gorden. NIDDK is active in the major NIH programs to recruit and retain minorities in biomedical research. Through the Minority Biomedical Research Support Grant (MBRS) mechanism (S06 grants), the NIDDK is supporting 25 projects at 18 institutions. While it is not possible to determine the ethnic background of each individual receiving support, many of the institutions involved have substantial or predominant Hispanic populations. These include the University of Puerto Rico, the University of California at San Diego, and the University of New Mexico, Albuquerque.

The NIDDK also supports Hispanics via the NIH Minority Supplement Award Program that provides for the addition of minority investigators to existing research grants. Currently the NIDDK is supporting 32 Hispanic students, pre- and post-doctoral trainees, and investigators through these mechanisms. In addition, NIDDK supports Hispanics on regular Institutional Training grants (T32s). Currently nine Hispanics are supported on NIDDK T32s.

Hispanic students at all levels are funded to attend the spring meeting of the Federation of Societies of Experimental Biology (FASEB) and the fall meeting of the American Physiological Society. Attendance at these meetings allows students to see the exchange of scientific information and offers opportunities for networking. Since 1985, NIDDK has conducted a workshop on research and research training opportunities at these meetings. In 1993, 11 Hispanic students received travel fellowships.

NIDDK has a summer fellowship program for Minority Access to Research Careers (MARC) scholars, and each year Hispanic students participate. In 1993, four Hispanic students were involved, and we expect five Hispanic students this summer.

At the Institute itself, we currently employ eight Hispanics in full-time and part-time equivalent positions, as well as seven Hispanics in non-tenured intramural positions.

HISPANICS IN CLINICAL TRIALS

Mr. Serrano. Fourth, what is your Institute doing to recruit and retain more Hispanics in clinical trials?

Dr. Gorden. The largest new clinical trial we are beginning is a major, multicenter clinical trial on the prevention of non-insulin dependent diabetes, the form of diabetes that disproportionately affects Hispanics and other minorities. In recruiting for this trial, we expect that over 50% of participants will be minorities. We will oversample Hispanics and other minority groups to ensure that their representation reflects the impact of this disease on these subgroups of the population.

We are also supporting some pilot clinical trials at research centers which are located in geographic areas where we expect to attain Hispanic participation. For example: we are funding a benign prostatic hyperplasia (BPH) pilot study that has centers at University of Texas and University of Colorado. The Mortality/Morbidity in Hemodialysis pilot clinical trial has a center at the UCLA Medical Center in Torrance, California. Consistent with NIH policy, when we issue research solicitations for clinical studies, we advise potential applicants of the need for appropriate inclusion of minorities and women in their study populations.

We have established a collaborative arrangement with the NIH Office of Research on Minority Health (ORMH) to enhance research in NIDDK research areas of particular relevance to minorities. I am pleased to report that, with financial support from that office, the NIDDK is supporting the following clinical research of relevance to Hispanics:

Gestational Diabetes Arm of the Primary Prevention of NIDDM trial. Most women who develop gestational diabetes will eventually progress to NIDDM at some time after their pregnancies. In particular, obese minority women with a history of gestational diabetes are at high risk of developing NIDDM. The trial aims to develop preventive interventions.

Pathogenesis of NIDDM in Mexican-American Women. This clinical study is examining the development of diabetes in Mexican-American women with gestational diabetes.

Diet Change in NIDDM Caribbean Latinos: A Team Approach. This study of urban Caribbean Latinos is focussed on developing and implementing a culturally-sensitive program to reduce dietary lipid intake to improve health outcomes in diabetics.

Education and Group Support for Diabetic Hispanics. The purpose of this study is to determine the efficacy of a culturally-relevant, community-based intervention aimed at improving the health of diabetic Mexican Americans in a rural Texas-Mexico border area.

Improving Metabolic Fitness in Obese Adolescents. In a racially mixed Colorado population, investigators will be developing a school-based intervention to optimize metabolic fitness and reduce the risk of metabolic diseases in obese adolescents.

HISPANICS IN RESEARCH

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Gorden. Information regarding the race and ethnic background of applicants for NIH research funds is kept centrally by the Division of Research Grants at the NIH (DRG), in order to protect the confidentiality of the investigators. In FY 1993, according to information provided to us by DRG, 52 Hispanics applied to the NIDDK for competing research grants, or 2.5 percent of the 2115 total competing applications we received. Nine of the Hispanic applications received awards, for a success rate of 17.3 percent. For the Institute as a whole, the overall success rate in FY 1993 was 22 percent, but the success rate for regular research grant applications reviewed by DRG study sections was 14 percent. The latter success rate excludes applications received in response to Requests for Applications (RFAs), which reserve funds for research in specific areas usually identified by the Congress for special emphasis. By this measure, Hispanics fared at least as well as the average applicant not responding to an RFA. Given the small numbers of Hispanic applicants, it is not possible to draw more substantive conclusions about their relative success.

The NIDDK is continuing to work to increase the participation of Hispanics in biomedical research through a number of mechanisms, including the Minority Biomedical Research Support Program, the NIH Minority Supplement Award Program, T32 Institutional Training Grants, funding for student attendance at scientific meetings, summer fellowship programs, and its intramural research program.

VITAMINS

Mr. Serrano. Dr. Gorden, the NIDDK budget justification mentions intramural work on determining the optimum dose of Vitamin C. Can you expand on that work -- and tell us what the optimum dose is? Do you have a view on the debate over FDA regulation of vitamins and other nutritional supplements, and do you think NIDDK's work will ultimately provide good information on optimal dosages?

Dr. Gorden. Research under way to develop means for determining optimum doses of vitamins is too preliminary at this time to state the optimum dose of vitamin C. Current investigations are providing good information on optimal dose for individual cells. However, once that is determined, it still remains to be ascertained how the amount of vitamin ingested by a person is translated into optimal cell dose. As to the debate over FDA regulation of vitamins and other nutritional supplements, NIH is a research and not a regulatory agency. Nevertheless, we would support FDA's position that there should be sufficient evidence before health claims are placed on labels of vitamins and supplements. In fact, the NIDDK is cooperating with the Office of Disease Prevention and Health Promotion in the Office of the Assistant Secretary for Health, the CDC, and the FDA in sponsoring a scientific workshop which will help establish what types of studies constitute adequate data in substantiating a health claim.

DIABETES CLINICAL TRIAL

Mr. Serrano. Dr. Gorden, please describe in more detail the clinical trial on preventing or delaying the onset of diabetes that you describe in your statement. What methods will NIDDK be testing? The justification says the study population for this trial will be 50 percent minority -- how will that break down among minorities?

Dr. Gorden. The NIDDK has begun a new and comprehensive initiative aimed at preventing diabetes and the complications it causes. This multi-faceted initiative encompasses basic and applied research, clinical studies and trials, and national multicenter trials conducted by the NIDDK, including a Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Prevention Trial. Risk factors for the disease include a family history of diabetes, obesity, insulin resistance, hyperinsulinemia, a history of gestational diabetes, and impaired glucose tolerance, with obese minority women particularly affected. The NIDDM Prevention Trial of preventive intervention strategies will be targeted at individuals with impaired glucose tolerance and a history of gestational diabetes and/or newly diagnosed NIDDM. Interventions may include diet, exercise, and pharmacologic agents. The trial will be conducted at 15 to 20 clinical centers and a data coordinating center. As you pointed out, Mr. Serrano, minority participants, including Hispanics, will make up 50 percent of the study population. Until patient recruitment is complete, we will not know precisely how it will that break down among minorities.

ISLET CELL TRANSPLANTATION

Mr. Serrano. Dr. Gorden, I am told that "islet cell transplantation" may have great potential as a treatment or cure for diabetes. Can you tell us the status of work on this method and what could be done to expedite or expand this work? Also, as I understand this islet cell research is dependent on human tissue resources, do you have the resources to support human and fetal pancreas transplant?

Dr. Gorden. Insulin is produced by the beta cells of the pancreas. The ability of the beta cell to secrete insulin in response to elevated blood sugar or glucose levels is crucial to survival. In insulin dependent diabetes mellitus (IDDM), the beta cells are destroyed by an autoimmune process. Hence, the IDDM patient requires exogenous insulin injections to survive. It is important to control both blood glucose levels and insulin levels in IDDM patients.

In light of the very positive results of the Diabetes Control and Complications Trial, new approaches to maintain normal blood glucose levels in IDDM patients are crucial. Researchers are developing new procedures and technologies, and progress is being made on a number of fronts. While no one approach has yet emerged that will clearly be the method of choice for insulin replacement, new developments in islet transplantation may offer an alternative to multiple daily insulin injections. Several methods are being investigated. One is whole pancreas transplantation, which requires major surgery and the administration of immunosuppressive drugs; it is unlikely that this approach will be applied to more than 1,000 cases per year. Another method is transplantation of isolated pancreatic islets, which also requires immunosuppression but entails a simpler surgery. It is limited by the amount of available tissue. Techniques for isolating, storing, and transplanting human islets will continue to develop. However, this approach may ultimately serve as an alternative insulin therapy for only a small fraction of IDDM patients.

Researchers are studying several methods to produce large numbers of pancreatic beta cells which can then be transplanted. Perhaps the most exciting approach is the development of immortalized beta cell lines. NIDDK grantees have reported success in "curing" diabetes in animals using genetically-engineered insulin-producing cell lines. This technology is being aggressively pursued.

Another aspect of islet and beta cell transplantation relates to protection of the grafted cells from rejection and immune destruction by the host. Ways around this problem include making the host tolerant to the graft by modifying or manipulating the host immune system or by using physical barriers, i.e. encapsulation, to shield the insulin-secreting cells from the host environment. These approaches, too, are being aggressively pursued.

New approaches to transplantation of beta cells or islets offer improved opportunities to treat IDDM patients. The NIDDK expects to pursue research efforts in all of these areas and other innovative strategies designed to achieve normal blood sugar levels in diabetic patients.

POLYCYSTIC KIDNEY DISEASE

Ms. DeLauro. Approximately how many researchers are working under NIDDK grants on PKD. How much money is allocated in FY '94 to this disease? How does that compare to NIDDK funding of other genetic diseases such as cystic fibrosis?

Dr. Gorden. NIDDK funding for PKD research in FY 1993 was $5.1 million. Those monies supported approximately 30 investigators. We estimate that PKD funding for FY 1994 will be approximately $5.3 million.

In FY 1993, NIDDK funding for cystic fibrosis (CF) research was $21.7 million; the FY 1994 estimate is $23.2 million. After the gene that is defective in most cases of CF was discovered in 1989, support for CF research increased greatly. At that time, a large pool of excellent investigators had already developed, and knowledge about the mechanisms of the disease had already reached a sophisticated level. For those reasons, the NIDDK, with advice from the community, concluded that an accelerated effort in CF research was warranted. Concomitantly, the Congress provided special funding emphasis for CF research to exploit the discovery of the gene.

We have not calculated the exact funding figures for other inherited diseases. However, we estimate them to be similar to, or less than, the funding for PKD.

CAPTOPRIL AND KIDNEY DISEASE

Mr. Bonilla. You mentioned in your testimony that the drug captopril has a beneficial effect on the kidney disease of insulin-dependent diabetes. Since FDA approved the drug in February, what has happened?

Dr. Gorden. The FDA's approval of captopril for the treatment of the kidney disease of insulin-dependent diabetes mellitus was based largely on evidence from a 30-center clinical trial funded by the NIDDK. In that study, captopril, a drug already approved for the treatment of hypertension and heart disease, reduced the risk of death or end-stage renal disease (characterized by the need for dialysis or renal transplantation) by 50 percent. Kidney disease was delayed or prevented for all study patients, regardless of degree of initial kidney impairment, and the protective effects of captopril were in addition to those seen by blood pressure lowering alone.

On April 4-5, 1994, the NIDDK sponsored a meeting at which nephrologists discussed the implications of results from three NIDDK-sponsored trials, including the captopril study. There was general agreement that the results of the captopril study should be incorporated into the clinical management of chronic renal disease resulting from insulin-dependent diabetes.

MINORITY PARTICIPATION IN THE NIDDM PREVENTION TRIAL

Mr. Bonilla. In your budget justification you state that minorities will make up 50 percent of the study population and the number and types of interventions tested will depend on the funds available. What effect will the .5 percent reduction in constant dollars have on your proposed preventive intervention strategies?

Dr. Gorden. As you know, Mr. Bonilla, the Institute will begin this major clinical trial to prevent non-insulin-dependent diabetes mellitus (NIDDM) in FY 1994. The trial will target the primary prevention of NIDDM in high risk individuals, including women with prior history of diabetes in pregnancy. This will be a collaborative effort between the NIDDK, the National Institute of Child Health and Human Development, and the NIH Office of Minority Health.

The funds that are projected to be available under the President's budget for FY 1995 for the Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Prevention Trial will support the testing and evaluation of interventions of the very highest scientific priority. That is, these interventions will provide what we believe to be the most important data in determining how best to prevent NIDDM. The way this trial is designed, any additional interventions that might be tested -- so called "arms" of the trial -- would add at least several million dollars each to the cost of the trial.

NIDDM PREVENTION TRIAL

Mr. Bonilla. Could you expand on your testimony dealing with the new NIDDK clinical trial aimed at preventing or delaying non-insulin-dependent diabetes? How big is the trial? How much will it cost? When will it be completed?

Dr. Gorden. Participants in the NIDDM Prevention Trial will be recruited at 15 to 20 clinical centers across the country. It will be the goal of each center to randomize approximately 200 participants into the study, for a total study population of 3,000 to 4,000. About one half the final recruitment number will be from minority groups. We estimate the total cost of the trial at between $75 million and $100 million. The trial will take about seven years to complete.

HISPANICS AND OBESITY

Mr. Bonilla. Do you think that the new clinical trial on "Longterm Outcome of Obesity Treatment in Minority Women" will have a large percentage of Hispanics? Again, how big is the trial? How much will it cost? When will it be completed?

Dr. Gorden. The trial you mention, to our knowledge, is the first culturally appropriate weight-loss intervention designed for African-American women. It will recruit 600 obese African-American women and is expected to cost about three million dollars total over the five years from 1993 until its end in 1997. Before this trial began, there had been no controlled clinical trials that examined weight loss and long-term weight control in African-Americans. This is despite the fact that obesity and obesity-related disorders are more prevalent in African-American women than in white women. The trial does not include other minority populations, because a major aspect of the intervention in the trial involves the participants sharing a common cultural frame of reference and support groups in order to minimize barriers to change.

It should be noted that several of the investigators involved in this study also are working with Hispanic women in other obesity trials, including the NIDDK-supported trial "Obesity Self-Management vs. Dependence Models."

DIABETES CONTROL AND COMPLICATIONS TRIAL

Mr. Bonilla. What is the NIDDK doing to "get the word out" on the results of the successful Diabetes Control and Complications Trial (DCCT)?

Dr. Gorden. The NIDDK is in the process of establishing a National Diabetes Outreach Program to help disseminate the results of the Diabetes Control and Complications Trial (DCCT). This trial demonstrated that close control of blood sugar levels can significantly prevent or delay serious complications of diabetes such as eye and kidney damage. The NIDDK will focus on dissemination of information from the DCCT to patients, health care professionals, and the general public regarding the importance of diabetes and the control of blood sugar levels. Presently, the Institute's Division of Diabetes, Endocrinology and Metabolic Diseases and National Diabetes Information Clearinghouse are developing the preliminary framework for this outreach program in coordination with voluntary health organizations in the diabetes community and other federal agencies.

DIABETES GENE INITIATIVE

Mr. Bonilla. How is the overall diabetes gene initiative coming along?

Dr. Gorden. Mr. Bonilla, this has been an exciting year for research on the genetics of diabetes. We have both initiatives and research advances to report.

To encourage research on the genes responsible for diabetes, the NIDDK recently implemented two initiatives. The objective of these initiatives is to encourage investigator-initiated research to develop and utilize new molecular genetic strategies to provide a better understanding of the major human genes involved in insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The first initiative was entitled "Genes Responsible for Insulin-Dependent Diabetes Mellitus." Seven grants were funded from this initiative. The second initiative, entitled "Human Genes for Non-Insulin Dependent Diabetes Mellitus," was implemented in collaboration with the American Diabetes Association. Eight grants were funded from this initiative. We look forward to reporting on the progress of these 15 grants next year.

Research on the genetics of diabetes was also intensified in FY 1991, when the NIDDK and Juvenile Diabetes Foundation International (JDFI) collaborated to establish the Institute's Diabetes Interdisciplinary Research Program (DIRP). The NIDDK awarded two program project grants as a result of this initiative. These projects incorporate an interdisciplinary research approach to the cause, course, and complications of IDDM, including a strong focus on genetics. Additional applications were funded by the JDFI. In FY 1993, the NIDDK issued a Request for Applications for recompetition of the DIRP grants, which will be funded in FY 1995.

The genetics of diabetes was the central theme of a July 1993 scientific conference the NIDDK and JDFI jointly sponsored. Representatives of the DIRP grants discussed research progress in this area. The participants included representatives of nine research programs including four supported by the JDFI and five supported by the NIDDK. This meeting enabled these researchers to exchange information and to foster collaborations with each other.

NIDDK-supported investigators are making great strides in understanding the genetic basis of both IDDM and NIDDM. I would like to describe two of these advances. Genetic analyses have confirmed the association between specific genetic characteristics and IDDM. It is also suggested that some characteristics primarily confer protection from disease to an individual who is a member of a high-risk population for IDDM while certain other characteristics confer susceptibility to disease.

Genetic studies of families with maturity-onset diabetes of the young (MODY), a type of NIDDM, have shown a close association between a particular portion of the gene responsible for a key enzyme involved in glucose processing and disease status. These "linkage" results imply that mutations in the enzyme gene itself may be the cause of diabetes in these families. Other studies have confirmed that a genetic mutation in this key regulatory enzyme of glucose processing can cause diabetes.

These examples highlight the rapid progress that is being made on the genetics of diabetes. Intensified genetics research offers great promise for understanding, controlling, and preventing diabetes. The NIDDK will continue to enhance support for both the basic understanding of diabetes and for the direct application of this knowledge to improve the health of diabetics.

POLYCYSTIC KIDNEY DISEASE

Mr. Bonilla. We hear that important progress is being made by some of your researchers working on matters related to Polycystic Kidney Disease. Would you tell us about that?

Dr. Gorden. Two studies were published recently that provide possible leads toward developing treatments to inhibit cysts in polycystic kidney disease (PKD). Both studies are very preliminary in terms of clinical practice, but they are both very encouraging. One study showed that cysts removed from PKD patients both absorbed and secreted fluid and that certain substances (both added substances and substances within the fluid itself) altered cyst formation. This means that it may be possible to develop drugs to alter net secretion of fluid from cysts and thereby inhibit cyst enlargement. In another study, mice that normally develop PKD and die from uremia by four to five weeks of age survived more than 200 days, with minimal loss of kidney function, after they were treated with taxol, a drug approved for the treatment of ovarian, breast, and lung cancers in humans.

DIABETES IN NATIVE AMERICANS

Mr. Bonilla. Diabetes is a major public health problem in Native Americans. Please describe the current investigations and the amount of resources being used to support this area of study.

Dr. Gorden. The NIDDK is continuing and enhancing its effort to combat non-insulin-dependent diabetes mellitus (NIDDM) in Native American and other minority populations, including Native Americans. Major efforts are ongoing in the Institute's extramural program, as well as at the Institute's field station in Phoenix, Arizona.

In FY 1993, the NIDDK initiated a program entitled "Diabetes in Native Americans and Alaska Natives" to develop and validate intervention approaches for the amelioration or prevention of NIDDM and its complications among American Indians and Alaska Natives. Eight grants were awarded as the result of this initiative; seven of the projects are studying various Indian populations. This regular research grant initiative was preceded by a planning grant programs in FY 1991. We look forward to reporting on the progress of these newest grants in the near future.

Researchers at the NIDDK in Arizona have been studying NIDDM in the Pima Indians for nearly 30 years. Results of these epidemiologic studies in a population group that has the world's highest reported prevalence of NIDDM have helped define the roles of various risk factors in the natural history of the disease. The studies have also indicated that genetic factors likely predispose certain individuals to NIDDM and probably also influence its severity and complications.

To give an idea of the kind of work the Institute is doing in Phoenix, I would like to tell you about an exciting advance that has developed over the past year. A you may know, more than half of the U.S. Pima population over the age of 35 years has NIDDM, and the cases are aggregated in families. Because of the high susceptibility of the Pimas to NIDDM, their relative genetic and environmental homogeneity, and the base of knowledge gained from long-term natural history studies of NIDDM in this population, the Pimas provide an excellent opportunity to increase understanding of the genetic underpinnings of the disease. NIDDK scientists have reported a strong association between measures of insulin action in Pima Indians and a region on chromosome 4. It appears that a small modification in a specific gene on this chromosome makes Pimas more resistant to insulin action, which causes them to be diabetic. This gene, therefore, may be a potential target for therapeutic interventions that might prevent or delay the onset of NIDDM.

In FY 1994, NIDDK support of research on diabetes and related research is approximately $196.8 million, and support of research relating to minority health is approximately $58.6 million.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

REQUEST FOR APPLICATIONS

Mr. Smith: Your budget describes focusing your research on a number of high priority areas, such as women's health and prevention. How do you plan to carry this out -- do you expect to issue a large number of requests for applications?

Dr. Gordis: In FY 1993, the NIAAA introduced six key research initiatives as priorities for decreasing alcohol abuse and alcoholism. To facilitate implementation of these initiatives in FY 1994 and 1995, the Institute issued a request for applications in each area of emphasis. These priority areas are Prevention, Women's Health, Minority Health, Alcohol and Youth, Health Services Research, and Medications Development. Applications are currently being received and awards are planned for FY 1994 and 1995.

Clearly gender differences exist in the human body's responses to alcohol consumption. Areas for study include the natural history, biological mechanisms, incidence and prevalence of alcohol use, abuse, dependence, and consequences among women and female animals. Of special concern are examining gender differences and identifying risk factors and markers that predict dependence and organ or tissue damage. In NIAAA's prevention initiative, emphasis is placed upon preventing fetal alcohol syndrome, alcohol-related problems in older populations, and non-traffic injuries.

Mr. Smith: Have you worked through the problems generated last year by the change in statute that limited the amount of services research that could be supported through the block grant and instead had to be picked up by your research budget?

Dr. Gordis: In the FY 1993 appropriation, NIAAA absorbed the costs of two services research projects: Project MATCH and the National Longitudinal Alcohol Epidemiologic Survey (NLAES) that were originally funded by the Block Grant Set-Aside (BGSA) of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). This change occurred due to the legislation, known as the ADAMHA Reorganization Act, transferring NIAAA to the National Institutes of Health, restructuring ADAMHA, and terminating BGSA support for services research projects as of fiscal year 1993.

The costs of these projects in FY 1993 were $5.2 million in total and were offset in the competing research project grant mechanism. While the Institute adjusted to this situation, this offset reduced our success rate.

MEDICATIONS DEVELOPMENT

Mr. Smith: How many drugs are currently in the pipeline in your medications development program?

Dr. Gordis: Twelve medications are currently being studied. Ten medications are being explored to reduce drinking including the opioid antagonists naltrexone and nalmefene, serotonin re-uptake inhibitors fluoxetine and sertraline, tricyclic antidepressants imipramine, desipramine, and nortriptyline, dopamine agonist bromocriptine, the anxiolytic agent buspirone, and lithium. Flumazenil, a benzodiazepine antagonist, is being tested for treating acute alcohol withdrawal. Finally, a pilot trial is being conducted with phosphatidylcholine, a polyunsaturated soybean lecithin, on alcoholics to prevent alcohol-induced liver fibrosis.

Mr. Smith: Has naltrexone reached the point in testing where it can be prescribed by clinicians?

Dr. Gordis: The only medication approved by the FDA to treat alcoholism is disulfiram (Antabuse). Naltrexone has not been approved for treating alcoholics. The positive results of naltrexone are based on recent results of two NIAAA-supported trials. To confirm and extend these studies, the Institute is currently funding new trials with naltrexone as well as one study with nalmefene, another opioid antagonist.

Mr. Smith: How many drugs have been identified but remain to be tested?

Dr. Gordis: Numerous previously FDA-approved psychotropic medications are available for testing in clinical trials. However, at this time, the NIAAA medications development program is funded at a level that permits research on the 12 medications mentioned previously.

WOMEN'S DRINKING

Mr. Smith: You are conducting a large longitudinal study of women's drinking. How many subjects are you following for how long a period?

Dr. Gordis: "Problem Drinking in Women: A National Longitudinal Study" is the largest and most in-depth longitudinal study of women's drinking conducted in the U.S. to date. The extension of this work will permit continuation of the survey research on the antecedents, dynamics and consequences of women's drinking.

The first sample was taken in 1981 and consisted of 911 women. At follow-up in 1991, researchers were able to study 696 of the original women and added a new sample of 403, bringing the total to 1,099. Scientists plan to follow up the sample again in 1996.

Mr. Smith: What new information is this study providing?

Dr. Gordis: Analyses are providing information on indicators of the onset of problem drinking, persistence of problem drinking, environmental risk factors, and the influence of marital status.

SUCCESS RATE

Mr. Smith: Your Institute has one of the higher success rates at NIH. What factors are responsible - mechanism mix, a smaller pool of investigators?

Dr. Gordis: In relation to other Institutes at NIH, NIAAA's number of applications for investigator-initiated research is small. However, in FY 1994 NIAAA is realizing a significant increase in the number of applications than previously estimated in research areas that the Institute has an expressed interest: Health Services Research, women's health, prevention, alcohol and youth, medication's development, and minority health.

PROJECT MATCH

Mr. Smith: Could you bring us up to date on your Project: Match treatment demonstration? When do you expect results to be available?

Dr. Gordis: The Project MATCH cooperative agreements are now in their fifth and final year. The study continues to complete the final follow-ups of clients and is analyzing preliminary data. Patient accrual was completed on April 30, 1993. A total of 1728 patients was entered, including ample representation of women (25%) and minorities (20%). Follow-up rates continue to be excellent and greatly exceed the usual rates obtained in studies of substance abusing populations.

Detailed analytic plans of matching outcome and process data are now being implemented. Results will be released in a phased manner, to assure that conclusions are announced only after all follow-ups are completed and the extensive data base is fully checked and edited. Now, analyses of a descriptive nature are being prepared; for example, validation of assessment instruments, baseline characteristics of the population and methodology. In late 1995 a preliminary report on results from early follow-up periods will be submitted to the Institute. Subsequently, more detailed reports on the complete follow-up periods will be prepared and published.

Major publications to date from the trial include a paper on the rationale and methods of the study published in the December 1993 issue of Alcoholism: Clinical and Experimental Research. A twelve chapter methodology monograph has been accepted for publication in the summer of 1994 as a special edition of the Journal of Alcohol Studies. Three manuals detailing the therapies used were published by NIAAA.

A review is in progress to determine if a three-year competitive renewal to fully extract maximal information from this unique and extensive data base will be funded, which would extend from September 1995 through September 1998, at which time the data base will become a public use tape, available for analysis by the alcoholism research community.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject areas of all research centers supported in 1994.

Dr. Gordis: In 1994, NIAAA is supporting 14 research centers at $18.7 million. These research centers have been established nationwide, and provide interdisciplinary research on different aspects of alcohol misuse. The research areas are as follows: Etiology and Treatment of Alcohol Dependence; Genetic Approaches to Neuropharmacology of Ethanol; Environmental Approaches to Prevention; Central Nervous System Effects of Alcohol: Cellular Neurobiology; Alcohol and the Cell; Fetal Alcohol Exposure (FAE): From Mechanism to Prevention; Genetic Determinants of Alcohol Ingestion; Metabolism of Alcohol and Associated Pathologic Effects; Epidemiology of Alcohol Problems; Alcoholism and the Aging: Brain Changes and Clinical Implications; Adolescent Alcohol Abuse: Biobehavioral Manifestations; Alcohol Treatment: Integrating Basic & Applied Research; Clinical and Medical Epidemiology of Alcohol; and, Alcohol, Infection and Host Response.

GENETIC ROLE IN ALCOHOLISM

Mr. Porter: Dr. Gordis, what role does genetics play in alcoholism?

Dr. Gordis: Substantial evidence indicates that genetic factors play a significant role in the development of at least some forms of alcoholism. The specific genetic factors underlying susceptibility to alcoholism and its complications remain to be elucidated. NIAAA is supporting the Genetics Cooperative Agreement (COGA), which is a large multi-disciplinary, multi-site collaborative study involving six extramural research study centers. Nearly 5,000 interviews of alcoholics and their family members have been conducted. Nearly 800 pedigrees have been established from 150 families, and cell lines from 1,300 individuals are available for genetic analysis. The COGA investigators will search the entire human genome for genetic markers which are linked to alcoholism. In the process of this search, they will be able to rigorously test the involvement of a number of genes hypothesized to contribute to susceptibility to alcoholism, and perhaps discover contributions from other genes not yet suspected of involvement with alcoholism.

Twin, family, and adoption studies have demonstrated that alcoholism can be inherited by both men and women. Twin studies compare the incidence of alcoholism in identical twins with the incidence of alcoholism in fraternal twins. If there is a genetic component in the risk for alcoholism, then identical twins, who have identical genes, would be expected to exhibit similar histories of developing (or not developing) alcoholism. Fraternal twins, who are genetically different individuals born at the same time, would be more likely to differ in their tendencies to develop alcoholism. In general, researchers using the twin method have found these expectations to be true.

Adoption studies may employ a number of techniques. One is to compare the histories of children of alcoholics who are adopted by nonalcoholics and grow up in a nondrinking environment with the histories of children of alcoholics similarly raised in a nondrinking environment. If genetic factors play a role, then the adopted children of alcoholics should preferentially develop alcoholism as adults. Evidence for these expected trends has been found by investigators.

Population and family studies attempt to establish the presence of a broad genetic influence on alcoholism. Different models for the way in which alcoholism runs in families have been suggested by a limited number of family studies. Interpretation of these studies has been complicated by the likelihood that alcoholism is a heterogeneous condition, that is, a collection of different conditions that look similar, but whose mechanism and modes of inheritance may differ. Additional studies are needed to sort out the mechanisms of transmission.

Possible genetic differences in the enzymes responsible for alcohol metabolism and elimination are also under study. Another area of major interest is defining the genetic risk factors for vulnerability to organ damage by alcohol.

PREVENTION ACTIVITIES

Mr. Porter: Please tell me about the NIAAA's activity on prevention.

Dr. Gordis: NIAAA prevention research will contribute to achieving the mission of the Institute by providing the basic scientific understanding, for example, to explain addiction and its mechanisms, which will consequently lead us to appropriate strategies for prevention. It will also help us learn how best to intervene with individuals who suffer from alcoholism and alcohol-related problems. In addition, it will provide the rationale for prevention strategies affecting the external environment, such as legislation and policy regarding presentation of the agent, drinking and driving, availability, and price.

Specifically, the NIAAA is supporting community prevention trials which were designed to capitalize on the knowledge base built by community-based research projects in the heart disease and cancer prevention fields. These trials are aimed at reducing youth access to alcohol and alcohol-related trauma, for example. NIAAA is also supporting research which examines the relative contribution of biological factors to the etiology of alcohol abuse and alcoholism and their inter-relationship with family, social, psychological, and environmental factors. Research is underway to determine the family, socio-cultural, legal, and other environmental triggers that can interact with individual vulnerability and result in alcohol abuse and alcoholism. Some other areas of high priority are Health Services Research, Fetal Alcohol Syndrome, Non-Traffic Injuries, and Special Populations, such as minorities, youth, women, and the elderly.

NIAAA spends approximately nine percent of its intramural research budget, fifteen percent of its extramural research budget, or 13 percent of its total research budget on prevention studies.

YOUTH AND ALCOHOL

Mr. Stokes: How extensive is the alcohol problem in children? What is the impact of alcohol abuse on their physical and psychological development?

Dr. Gordis: Of all the drugs of abuse, alcohol continues to be used and misused by a greater proportion of children and adolescents (through age 18) than any other drug on a daily basis. Although most high school seniors cannot legally buy alcoholic beverages, 90 percent in 1990 had tried alcohol, compared with 64 percent who had tried cigarettes, and fewer still who had tried illegal drugs[1]. An ongoing study at the University of Michigan, Monitoring the Future, has tracked adolescent alcohol and illegal drug use since 1975. Daily alcohol use was the highest in 1979, and has been slowly decreasing since that time. However, self-reports of daily drunkenness have not shown a comparable decrease, and the prevalence of reported binge drinking (5 or more drinks in a row within the last 2 weeks) among high school seniors has remained around 28 percent. Of great concern is information that binge drinking increased among 10th graders from 21.1 percent in 1992 to 23.0 percent in 1993. The rate of binge drinking for 8th graders remained around 13 percent[2].

The physical consequences of alcohol misuse and abuse can be observed in children at birth. Alcohol is a teratogen capable of inducing congenital defects, growth retardation, learning disabilities, and other behavioral disturbances. Alcohol's adverse effects on the fetus exist along a continuum, with complete Fetal Alcohol Syndrome (FAS) at one end of the spectrum and incomplete features of FAS, including more subtle cognitive-behavioral deficits, on the other. Among children and adolescents who use alcohol but may not have been exposed in utero, there is the risk of delayed puberty among frequent drinkers, risky sexual behavior, alcohol-induced disinhibition and impairment of judgment, reduced testosterone levels in males, menstrual-cycle disturbances and the potential for spontaneous abortion[3] in females. Finally, there is an increased risk for unintentional injury, trauma, and death due to alcohol misuse by children and adolescents.

The psychological consequences of alcohol use and misuse among children and adolescents can be observed in poor school performance, low commitment to school, increased risk of dropping out of school, incomplete learning of social skills (especially communication and decision-making skills), and reinforcement of patterns of behavior which may cause problems in the child's later adult life[4].

Thus, misuse and abuse of alcohol by children and adolescents can have serious, and sometimes fatal consequences. Alcohol abuse can have negative physiological effects on growth and development, learning ability, and general health. And it can affect the psychological and social development of children and adolescents as reflected in their expectancies, behaviors, and interactions.

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2. Johnston, L.D., O'Malley, P.M. and Bachman, J.G. (1994). Drug abuse among American high school seniors,, college students,, and young adults, 1975-1993. Washington, D.C.: Superintendent of Documents, U.S. Government Printing Office. (Table 5 and page 3, Press Conference handout).
3. NIAAA, Op.Cit.., pp. 178-179.
4. NIAAA, Ibid., pp. 268-269.

BIRTH DEFECTS

Mr. Stokes: With regard to alcohol-induced birth defects, what is relationship between alcohol and vitamin A? How extensive is this problem? Is the Institute collaborating with the National Institute of Child Health and Human Development on this research?

Dr. Gordis: Retinoic acid is the active metabolite of vitamin A and plays a central role in embryonic development as a regulator of gene expression during differentiation of the structures of the neural crest. Disturbances of retinoic acid homeostasis, i.e., maternal vitamin A excess or deficiency, can lead to malformation of the fetus. There is no information available on the prevalence of vitamin A deficiency among alcohol abusing pregnant women, or whether maternal alcohol consumption during gestation alters the retinoid status of the fetus. The only direct laboratory evidence of ethanol as an agent that can perturb retinoid homeostasis consists of inhibition of the conversion of retinol to retinoic acid by ethanol *in vitro*. Since one of the human enzymes for ethanol metabolism, alcohol dehydrogenase, ADH3, appears to be involved in both retinol and ethanol oxidation -- and ALDH in retinal and acetaldehyde metabolism -- ethanol at high doses may inhibit retinoic acid synthesis *in vivo* through competitive inhibition. Ethanol-induced congenital defects may be due to ethanol reducing the amount of retinoic acid in the developing embryo to a level which can no longer properly regulate target genes such as those of the neural homeobox gene family and other retinoid regulated genes.

This is an attractive hypothesis for ethanol teratogenesis and is one of several which are being explored by the scientific community. We plan to explore collaboration with NICHD on this research as it evolves.

GENETIC AND ENVIRONMENTAL FACTORS IN MINORITIES

Mr. Stokes: Do we know what genetic and environment factors make minorities more susceptible to alcohol diseases?

Dr. Gordis: The precise genetic and environmental factors that make minorities susceptible to alcohol-related diseases are under investigation. Variations in drinking patterns and drinking problems have been noted among different racial and ethnic groups for over 20 years. For instance, African-Americans are at high risk for the alcohol-related diseases liver cirrhosis, fatty liver, hepatitis, heart disease, certain cancers, and fetal alcohol syndrome (FAS). Some studies suggest that Hispanic males have higher rates of alcohol dependence and other alcohol-related problems, such as drinking and driving fatalities, than Caucasian males. The Native American/Alaskan population is a young, diverse, rapidly growing group living in urban, rural, and reservation settings. Although alcohol use varies widely among tribes, of those who drink heavily, alcohol abuse is a major factor in death from accidents, chronic liver disease and cirrhosis, homicide, suicide, and FAS. Research on Asian-American alcohol use and abuse indicates low rates of alcohol-related problems even among those identified as heavy drinkers. This has been attributed to ethnic differences in physiological reactions, e.g., the "flushing response", as well as socio-cultural and environmental factors. Alcohol consumption in Hispanics and Asians increases with successive generations born in the U.S. and also as acculturation progresses in immigrants.

The reasons for the observed differences among various racial populations are not yet known. Genetic variability in alcohol metabolizing enzymes, collagen production, cytokine production, utilization of choline and vitamin A or depletion of glutathione and vitamin E may contribute to the increased susceptibility of certain minorities to alcohol diseases. Environmental factors such as pattern of drinking, socioeconomic factors, nutrition, and medication may also play an important role. In addition to our current portfolio, NIAAA was issued an RFA in October 1993 entitled "Alcohol and Minorities: Biomedical and Behavioral Research." Grants awarded under this RFA are expected to increase our understanding of how variations in drinking patterns and responses to alcohol among diverse cultural and ethnic-subgroups can serve as the basis for the development of more effective treatment and intervention strategies for specific populations. A second program announcement "Preventing Alcohol-Related Problems Among Ethnic Minorities" was issued in February of 1993. This program announcement focuses on the culturally-appropriate development or adaptation of interventions within minority settings, and how ethnic minority identity relates to prevention research outcomes.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly. How much is included in the FY 1995 budget request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Gordis: Alcoholism is a complex disease influenced by individual physiology, psychology, and the environment. Although most alcohol-metabolizing enzymes are encoded by single genes or families of related genes, alcohol-related behaviors, such as sensitivity, tolerance, dependence, or withdrawal, are much more complex. People differ quantitatively in such behavioral traits, rather than in an all-or-none fashion. At this point in time, because of these complexities, it is premature for this Institute to invest in gene therapy protocols. In the future, however, it may be possible to intervene genetically with the disease of alcoholism. As the genes that define enzyme subtypes and other physiological processes, such as the development of organ damage, are identified, it may be possible to fashion a genetic therapy that will intervene with the disease process. At some really distant point in the future, it might be possible to identify those persons at risk for developing alcoholism and use gene therapy to alter their risk.

MINORITY HEALTH CRISIS

Mr. Stokes: As the Director of an Institute of the NIH, the nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues -- while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and -- while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Gordis: In the area of alcohol research, NIAAA studies suggest that minorities suffer disproportionately to many of the disorders due to alcohol misuse. For example, African-Americans may have a genetic predisposition to alcohol-related liver disease, and many Native American communities suffer an alarming rate of Fetal Alcohol Syndrome. NIAAA acknowledges the disparity of minority health with the major portions of the population at a time of scientific advancement, and is attempting through its research to alleviate the problems that alcohol causes minority populations.

Because of the health problems that minorities face with alcohol misuse and related medical disorders, NIAAA issued in FY 1994 a Request for Applications (RFA) on Minority Health, and a RFA on Prevention that includes minority health issues. In the FY 1995 request, NIAAA would provide support of $24.5 million for minority health concerns, a 9 percent increase over the FY 1994 level.

RESEARCH OPPORTUNITIES AND BENEFITS

Mr. Stokes: What are some of the most exciting and most promising basic research opportunities at your Institute? Elaborate on the benefits to be achieved from further investments in this research.

Dr. Gordis: We believe the following areas are most promising and will have the highest payoff.

Markers for Identifying Individuals at High Risk for Alcoholism: A major aim of the basic research program is to develop methods to measure an individual's vulnerability to developing alcoholism and related medical sequelae. It is important for these measures, or markers, to have high predictive value. Studies of male children of alcoholics have suggested that measures of sensitivity to the administration of alcohol or of certain electrical changes in the brain can predict subsequent alcoholism among these children. Increased levels of a specific protein, Gsα, in erythrocyte and lymphocyte membranes found in nonalcoholic men who were born into families with alcoholic member(s) may be another such marker. Research along this line will allow for the early identification of and early intervention with individuals at high-risk for developing alcoholism.

Genetic Mapping: Alcoholism is a complex disease with various genetic and environmental factors which influence the development and ultimate expression of the disorder. Genetic mapping of quantitative trait loci (QTLs) contributing to alcoholism and alcohol responses is a relatively new and exciting research area. This technique gives the investigator the ability to define the contribution of a single gene to complex behaviors that are determined by the interaction of many genes and for which environmental factors are important. QTL mapping employs genetic crossing of inbred rat or mouse strains and achieves statistical power by using a sufficient number of animals. Because of the conservation of gene order during mammalian evolution, many syntenic regions between these species have been identified. Many genetic markers are becoming available that can be screened for their contribution to the expression of the complex behaviors associated with alcoholism. Once linkage is established, candidate genes in animals and humans can be identified by comparative mapping. Thus, dissection of complex polygenic traits in an animal model is leading to a rapid and effective way of identifying important genes contributing to various responses to alcohol and the susceptibility to alcoholism in humans.

Genetics of Susceptibility to Alcohol-Induced Organ Damage: Only a relatively small proportion of alcoholics become affected by medical complications of alcoholism (e.g., liver cirrhosis, pancreatitis, cardiomyopathy, Wernicke-Korsakoff's Syndrome), and different individuals succumb to different complications. Large individual differences also occur in the incidence and severity of fetal alcohol syndrome (FAS) in the children of mothers who drink during pregnancy. Characterization and isolation of genes underlying susceptibility to alcohol-induced organ damage will allow early identification of individuals at risk. The genetic information will help improve the design of studies of environmental factors conducive to these disorders. It may ultimately improve pharmacotherapy for these disorders by facilitating the design of drugs which interact with the products of these genes.

The Mechanisms of Uncontrolled Alcohol Intake: The most crucial issue in alcohol research today is why some people drink uncontrollably. Uncontrolled alcohol intake results from a complex interaction among genetic, biological, and environmental factors. Several neurotransmitters have been identified as possible candidates for mediators of alcohol reinforcement; the two most important of which are dopamine and serotonin. Research on the molecular mechanisms of the reinforcing effects of alcohol on the brain, motivated drinking, and satiety is integral to understanding uncontrolled appetitive behavior, such as uncontrolled consumption of alcohol and eating disorders. Recent evidence suggests a link between eating disorders and alcoholism. Bulimic patients show an addiction-like behavior (craving, loss of control, adverse social and medical consequences) and often tend to abuse alcohol or other drugs. Animal and human studies on how the presence of alcohol alters appetitive behaviors after acute and chronic exposure, and how these behaviors are augmented or diminished by environmental cues and stress are also quite important. The resulting knowledge will broaden the scope of therapeutic interventions that can be used to reduce the reinforcing effect or craving for alcohol which will aid in the treatment of alcoholism, including the incidence of relapse.

Alcohol, Estrogen and Women's Health: Alcohol is known to increase estrogen levels and alter the ratio of estrogen to other hormones. Estrogen and its receptors are known to be involved in the regulation of many cellular processes. Basic research to explore a possible causal relationship between alcohol consumption and altered hormone status in the etiology of alcohol-related medical complications such as liver disease among women is needed. Understanding how alcohol interacts with the endocrine system at the cellular and molecular level will aid in our understanding of how pathogenesis is accelerated in women. This may lead to the development of specific hormonal therapies to prevent alcohol-related pathology in women.

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Gordis: There are concerns in the scientific community about the level of resources and the development of programs to encourage interest in research careers. Recent efforts to implement a science education grant program at NIH for the elementary and secondary school levels is in response to these concerns.

At NIAAA, we are concerned also about the number of physicians entering research careers and the number of research trainees. In 1994 appropriation, NIAAA was able to increase its support for research careers with special emphasis on physicians, and research trainees for the first time since FY 1990. Needs that we are starting to address include training in areas of genetics, health services research, and the neurosciences. In the FY 1995 request, NIAAA would provide current services for research careers and research training.

CLINICAL RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your Institute. Elaborate on the benefits to be achieved from further investments in this research.

Dr. Gordis: As evidenced by our investment in the Project MATCH cooperative agreement, the concept of matching alcoholic patients to the most effective treatments for their particular needs and characteristics holds much promise. This is important because we now know that the disorder of alcoholism is extremely heterogenous in its causes, manifestations, and consequences. The persons afflicted have a wide range of social, personal, psychological, economic, and familial characteristics that make their treatment needs highly individual. This diversity of the disorder itself and of the circumstances of patients afflicted means that selection of the optimal therapy from among the many available psychosocial and pharmacologic treatment modalities requires a set of carefully defined and tested "rules" or guidelines for treatment assignment.

Research on pharmacologic treatment of alcoholism has dramatically expanded at NIAAA over the past five years. In particular, advances have been made in developing medications that decrease the desire to drink. The most promising medication appears to be the orally active opioid antagonist, naltrexone.

Two recent clinical studies of naltrexone on alcohol dependent patients have shown it to be effective in attenuating the level of craving for alcohol, reducing the frequency and amount of drinking, and decreasing the rate of relapse. Interestingly, if patients do "slip" and have one or two drinks, those on naltrexone are less likely to continue drinking than are placebo-treated subjects.

In addition to naltrexone, other pharmacologic agents appear promising. These include nalmefene, another opioid antagonist and the serotonin re-uptake inhibitors fluoxetine and sertraline. Numerous other pharmacologic medications are currently being explored in animal models. Because the biological bases for drinking behavior involves several neurotransmitter systems there are numerous possibilities for new promising medications.

The benefits to be gained from pursuing matching and research both of psychosocial, pharmacologic and combined therapies affect the patient, his/her family and society at large. The improvement in the quality of life, as well as the physical morbidity and mortality than can be associated with excessive alcohol consumption, cannot be overestimated. We know that the effects of alcoholism upon the family and especially on children are profound, and that many of the behavioral and psychological sequelae are multi-generational in scope. The benefits to society in the short term include greater efficiency, and perhaps cost savings, in the treatment of alcoholism, as well as the elimination of adverse consequences for generations to come.

MINORITY RESEARCH AND RESEARCH TRAINING

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Gordis: In FY 1994, NIAAA issued a special RFA for grant proposals to study the medical and behavioral consequences of alcohol consumption on minority groups and individuals including the development of more effective treatment and prevention approaches. With regard to support minority research training we routinely hold technical assistance workshops for minority investigators, and provide grant support through several mechanisms designed to encourage and promote the development of minority researchers.

In the FY 1995 request, NIAAA would provide $24.5 million for minority health research and $1.8 million for minority training. Together, this support reflects an increase of 8.6 percent over the FY 1994 level.

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your Institute?

Dr. Gordis: In terms of minority health research initiatives, NIAAA issued an RFA in October 1993 entitled "Alcohol and Minorities: Biomedical and Behavioral Research." Grants awarded under this RFA are expected to increase our understanding of how variations in drinking patterns and responses to alcohol among diverse cultural and ethnic-subgroups can serve as the basis for the development of more effective treatment and intervention strategies for specific populations. A program announcement entitled "Preventing Alcohol-Related Problems Among Ethnic Minorities" was issued in February of 1993. This program announcement focuses on the culturally-appropriate development or adaptation of interventions within minority settings, and how ethnic minority identity relates to prevention research outcomes.

Regarding research training and outreach, NIAAA participates in the NIH-wide minority training programs, MARC, MIRDP, MBRS, funding of HBCUs, administrative supplements, and special pre-doctoral minority fellowships. Technical assistance workshops are also conducted for the benefit of minority researchers.

Mr. Stokes: How does your Institute identify its priorities for investments in minority research and research training?

Dr. Gordis: NIAAA staff is in contact with Institutions and persons involved in promoting minority research, identifying minority investigators, and promoting minority research training. Through these discussions we learn of opportunities to further our involvement in minority research and research training. We are also in contact with the NIH Office of Research on Minority Health.

Mr. Stokes: When your Institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health? To what extent is there a collaborate relationship between the two organizations? Elaborate.

Dr. Gordis: NIAAA does seek advice from the Office of Research on Minority Health (ORMH) in our efforts to strengthen research on minority health. Our collaborative relationship with ORMH has resulted in the opportunity and support for the recruitment of minority students for research on active research grants as well as support for a workshop on technical assistance for interested minority students.

CLINICAL TRIALS

Mr. Stokes: How much is included in the FY 1995 budget request for clinical trials? How does this amount compare with the amount invested in clinical trials in FY 1994, and FY 1993?

Dr. Gordis: Clinical trials funding for FY 1993 was $17,550,000; for FY 1994 the estimate is $18,400,000; and for FY 1995 it is $19,100,000.

Mr. Stokes: Would you please comment on the economic benefits, and the quality of life benefits of some of the major clinical trials supported by your Institute?

Dr. Gordis: As evidenced by our largest treatment research initiative, Project MATCH, we feel there is great promise in the concept of matching alcoholic patients to the most effective treatments for their particular needs and characteristics. This is important because we now know that the disorder of alcoholism is extremely heterogenous in its causes, manifestations and consequences. The persons afflicted have a wide range of social, personal, psychological, economic, and familial characteristics that make their treatment needs highly individual. This diversity of the disorder itself and of the patients afflicted means that selection of the optimal therapy from among the many available psychosocial and pharmacologic treatment modalities requires a set of carefully defined and tested "rules" or guidelines for treatment assignment.
The benefits to be gained from pursuing matching research, both for psychosocial, pharmacologic and combined therapies affect the patient, his/her family and society at large.

In addition to treatment clinical trials, NIAAA is also sponsoring prevention interventions. The joint NIAAA/OSAP community prevention trials are aimed at reducing youth access to alcohol -- the Heartland Project -- and reducing alcohol-related trauma -- the Trauma Reduction Trial. The Heartland Project is a randomized study of interventions to reduce youth access to alcoholic beverages. It involves 18 Minnesota communities --nine experimental and nine control -- where the community itself is the unit of analysis. The Trauma Reduction Trial is an efficacy trial of interventions to reduce alcohol-related trauma in two matched pairs of communities. One pair consists of Salinas and Modesto, California as intervention and control communities, respectively. The other pair consists of two counties in South Carolina -- Florence County is the intervention community, and Sumter County serves as the control community.

The improvement in the quality of life, as well as the physical morbidity and mortality than can be associated with excessive alcohol consumption, cannot be overestimated. We know that the effects of alcoholism upon the family and especially children are profound, and that many of the behavioral and psychological sequelae are multi-generational in scope. The benefits to society in the short term include greater efficiency, and perhaps cost savings, in the treatment of alcoholism, as well as the alienation of adverse consequences for generations to come.

Mr. Stokes: To what extent has the Institute increased the number of minorities participating in its clinical trials? What progress is being made?

Dr. Gordis: Using our largest multi-site clinical trial, Project MATCH, as an example, the investigators made active efforts to recruit minorities at all sites. During the planning phase, a goal was set of 20% minorities. Strategies were devised to attract and retain minority groups into the trial which ultimately proved effective, in that this goal was met. Of the total of 1728 patients recruited, 342 (or 20%) are minorities. Of this, 169 (9.8%) are African American; 143 (8.3) are Hispanic, and 30 (1.7%) are other minority groups such as Native American, Asian, Alaskan American, etc.

MINORITY SUPPLEMENT

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Gordis: NIAAA began awarding minority supplements in 1989. Applications for research project grants from participants in the supplement program are beginning to be received. Considering the time involved in preparation for a research career and that the majority of minority supplements are awarded to students in early phases of graduate education, we would anticipate receiving applications 4 to 5 years after the initial supplement award.

HISTORICALLY BLACK COLLEGES

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of historically black colleges and universities in biomedical research?

Dr. Gordis: NIAAA actively supports a number of programs aimed at increasing the participation of historically black colleges and universities in biomedical research. NIAAA continues to provide support for students and faculty from HBCUs to obtain research experience through administrative supplements awarded to active grantees. The Institute participates in the MBRS program with emphasis on encouragement of HBCU investigators to submit proposals that contain specific sub-projects to address alcohol related research areas and encourages collaboration between HBCU scientists and scientists in majority institutions. NIAAA also participates in the special pre-doctoral fellowship program for minority students, has renewed emphasis on the availability of faculty fellowships (F-34) for minority investigators, and contributes to the MARC program.

EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Institute, and how many employees in your Institute are in GS-15 and above positions?

Dr. Gordis: There are 36 GS-15 positions and above in NIAAA. There are 35 employees in GS-15 and above positions.

Mr. Stokes: In your Institute, currently, how many African Americans are at the GS-15 and above level, and in what positions are they?

Dr. Gordis: There is 1 African-American. She holds the position of Chief, Planning and Financial Management Branch.

Mr. Stokes: In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Gordis: At this time, NIAAA has no cases pending for exceptions to the hiring freeze.

Mr. Stokes: Has the NIH requested relief from the freeze, and, if so, what was the response?

Dr. Gordis: NIH has requested relief from PHS on the hiring freeze, but there has been no formal response from PHS on the matter.

Mr. Stokes: If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Gordis: Although NIAAA hiring would be limited because of the Institute's personnel ceiling, NIAAA continually encourages minorities to consider employment and career opportunities at NIAAA, through job announcements, job fairs, and mailings to minority organizations. We also have a major interest in attracting minority scientists and clinicians to our IRP.

PREVENTION RESEARCH INITIATIVES

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Gordis: NIAAA has an exciting and innovative ongoing program in prevention. For example, we are currently supporting investigations on community intervention trials; reducing youthful consumption of alcohol; the effect of alcohol consumption on AIDS-related high-risk behavior; and the impact of drunk driving laws and other policy-related issues. In addition to our current active portfolio, in October 1993 we issued two new RFAs directed towards prevention research. The first is titled: "Underdeveloped Areas of Alcohol Abuse Prevention Research." This RFA is seeking proposals to conduct studies focused on the prevention of 3 types of alcohol-related problems where prevention has received very little research attention: fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE); alcohol abuse among the elderly; and non-traffic, alcohol-related injuries -- drownings, burns, falls, trauma to pedestrians, and injuries incurred in crashes of planes, boats, and trains. The major task is to develop and test interventions aimed at preventing these problems before they occur.

The second RFA with major prevention significance is titled: "Health Services Research on Alcohol-Related Problems." The intent of health services prevention research is to assess the effectiveness of preventive interventions in reducing alcohol-related problems and/or contributing risk factors. In addition to intervention studies in health care settings, prevention services research may occur in a variety of other settings, e.g., worksites, schools, and local communities, and may focus on financing, organization, management, enforcement, and utilization of prevention services as well as their effectiveness.

BIOTECHNOLOGY

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Gordis: NIAAA is clearly benefitting from research in biotechnology. As is often the case in science, basic research provides spin-off opportunities not even imaginable when the original research is first begun. Today, advances in molecular biology and genetics has great relevance to alcohol research in our quest for understanding of the heredity and the physiology of alcoholism. Advances in molecular biology and genetic techniques, such as linkage studies, targeted gene disruption, genome scanning, and quantitative trait loci mapping are making it possible to identify the genes responsible for conferring vulnerability to alcoholism and alcohol-related disease.

Studies of human families and their patterns of inheritance are central to defining the observable characteristics of the disease, e.g., age of onset, frequency of drinking, that are strongly heritable. Molecular biology takes the investigation to the level of the individual gene or clusters of genes. Linkage studies look for patterns of inheritance where trait A is always present when gene B is present. These traits are then markers and are said to be "linked." Using molecular biology techniques, the human genome project is assembling many markers into a dense map of the human genome. This dense map is essential for linkage studies which provide the methodology for identifying genes underlying alcoholism. Identifying these genes is an important goal in the study of the human genetics of alcoholism -- a goal that eventually can lead to a systematic approach to preventing and treating alcoholism.

MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Gordis: In FY 1994, NIAAA will provide an estimated $1,980,000 to support minority institutions. In FY 1995, the Institute has requested $2,070,000 in support, a 4% increase.

Mr. Stokes: Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Institute's programs and activities.

Dr. Gordis: NIAAA efforts focus on assisting interested faculty to enhance their ability to be competitive in obtaining research support through special and existing grant programs. The Institute encourages investigators to utilize mechanisms such as small grants, AREA grants, and faculty fellowship awards. Technical assistance workshops for minority applicants are held to assist them in developing grant writing skills and program staff maintains personal and informal communication to encourage collaboration with established investigators. Staff assistance visits to HBCUs and other academic institutions with substantial minority enrollment are well received and productive. NIAAA participates in minority conferences and workshops through financial support and attendance.

UNDERREPRESENTED MINORITIES IN RESEARCH

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Gordis: The FY 1995 increases requested by NIAAA would enable the Institute to expand involvement beyond current level of support of programs specially designed to assist minority individuals. Additional resources would enable NIAAA to conduct staff assistance visits and provide consultation to minority institutions. We would like to expand research training resources to commit support beyond the current level in the predoctoral minority fellowship program.

ALCOHOL AND CANCER

Mrs. Lowey: What can you tell the Committee about the connection between alcohol abuse and cancer -- What does the latest research tell us? What about more moderate use of alcohol?

Dr. Gordis: Most studies to date are epidemiologic and at best show a positive association of alcohol with the development of specific cancers. Some epidemiologic studies in humans have associated the use of alcohol with the development of precancerous colon polyps, breast, oral, and esophageal cancer. Part of the difficulty with such studies is the large number of confounding factors -- diet, smoking, family history, parity, and so on -- present in most subjects. Because of these complex interactions, results are difficult to interpret and thus much additional research needs to be conducted.

WOMEN AND ALCOHOL STUDIES

Mrs. Lowey: What is the Institute's policy with respect to ensuring the inclusion of women in studies of alcoholism?

Dr. Gordis: The Institute fully adheres to the NIH-wide policy of inclusion of women in clinical trials as expressed in the NIH Guide to Grants. However, prior to the initial promulgation of the guidelines, NIAAA was conscious of the need to enhance the representation of women in clinical trials. Thus, Project MATCH, which was funded before the original guidelines were in force, set goals for the inclusion of women early in its planning. As a result, 430 female patients out of a total 1,728 have been enrolled. This is good representation considering the difficulty in recruiting and retaining women in this type of clinical trial. This level of participation provides an important opportunity to examine gender differences in alcoholism treatment. NIAAA has supported and participated in the first and second rounds of Office of Research on Women's Health grant supplements for this purpose, and program staff have recently served on an NIH review committee developing the "Outreach Notebook" which will provide guidance to the general scientific community on implementation of the policy.

Mrs. Lowey: Can you describe briefly the NIAAA's plans for expanding its research on alcohol's role in elevating risk factors for diseases in women, such as heart disease, breast cancer, and stroke?

Dr. Gordis: NIAAA has long recognized that there are gender differences in onset and severity of alcohol-related medical problems and has always had a strong commitment to research on women's health. In fact, 11% of the Institute's research portfolio related to human subjects focuses specifically on women's health issues.

Recent ongoing NIAAA activities include a symposium on "Gender Differences in Animal Studies: Implications for the Study of Human Alcoholism", presented at a meeting of the Research Society on Alcoholism, in June 1993 to stimulate interest in research on gender differences in animal models. Also, the NIAAA has developed several program highlights on a variety of topics related to the etiology of alcoholism and medical consequences. Three recently developed program highlights encourage basic research specifically related to women's health issues: gender differences in alcohol intake, female reproduction, and medical consequences in women. In addition, the NIAAA has issued a Request for Application which solicited research grant applications on a wide range of topics related to alcohol and women's health. Applications have been received and will be reviewed and funded in late FY 1994 and FY 1995.

In addition, NIAAA is actively participating in the NIH Women's Health Study, the largest clinical study of women's health ever undertaken in the history of the NIH. Gender differences in the impact of alcohol consumption on heart disease are of particular interest. Staff input into the design and content of the alcohol portions of the survey research instruments will enable researchers to examine the role of alcohol consumption in breast cancer, reproductive cancers, heart disease and osteoporosis and should provide major contributions to the field of alcohol research.

Mrs. Lowey: Can you update the Committee on the progress of the Institute's longitudinal study of women's drinking?

Dr. Gordis: NIAAA is supporting a study, "Problem Drinking in Women: A National Longitudinal Study" which is the largest and most in-depth longitudinal study of women's drinking conducted in the U.S. to date. This project is providing scientific data on the antecedents, dynamics, and consequences of women's drinking. This study will yield information over a long period of time in such areas as indicators of the onset of problem drinking, persistence of problem drinking, environmental risk factors, and the influence of marital status.

SCHOOL-BASED PREVENTION

Mrs. Lowey: Your testimony refers to the findings of an Institute-supported study of the effectiveness and efficiency of preventive programs. Can you tell the Committee what that study indicates in the area of school-based prevention programs?

Dr. Gordis: There are two good, recent reviews of what is effective in school-based prevention. One is contained in the Institute's Eighth Report to the U.S. Congress on Alcohol and Health. The other was written by Dr. William Hansen and was published in Health Education Research.[1] These reviews indicate in general that there are three types of programs, those which focus on affective education, those which focus on social influences, and comprehensive programs. Affective education based programs, a category that includes values clarification, stress management, self-esteem enhancement, and decision-making skills, seem to have little impact on alcohol use. Programs focusing on social influences -- of which the two most important have been peer resistance training and education about perceived norms surrounding alcohol use -- have shown promise for changing alcohol use patterns. Comprehensive programs, i.e., programs that include a broad range of prevention strategies, including social influences, have achieved positive results on preventing alcohol misuse.

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[1] Hansen, William B. 1992. School-Based Substance Abuse Prevention: A Review of the State of the Art in Curriculum, 1980-1990. Health Education Research Vol. 7, No. 3, pp. 403-430.

HISPANIC ISSUES

Mr. Serrano: Dr. Gordis, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions.

First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Gordis: The NIAAA continually encourages hiring of Hispanics through job fairs and mailings of career opportunities with promotion potential to Hispanic organizations. However, our efforts have been restricted during FY 1994, since NIAAA is subject to a hiring freeze due to the administration's efforts to reduce the number of Federal employees.

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Gordis: Approximately 4% of the NIAAA budget supports studies directed at Hispanic health issues.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Gordis: NIAAA funded several programs to increase the participation of Hispanics in biomedical research. In particular, the Institute supports the Minority Access to Research Career, the Minority Biomedical Research Support, and the Minority High School Summer Student Research Apprenticeship programs, and research supplements for minority students to encourage Hispanics to pursue research careers.

Mr. Serrano: Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Gordis: Using our largest multisite clinical trial, Project MATCH, as an example, the investigators made active efforts to recruit Hispanics at all sites. In particular, some of the sites are located in parts of the country where large Hispanic populations are present, such as Albuquerque and Houston, where 46% and 9%, respectively, of the sample is Hispanic. Overall, 8.3% of the study sample is Hispanic, (143 subjects). A subproject was included in which an acculturation scale was developed and administered to the Hispanic subjects. The results of this subproject will better enable investigators to interpret the findings from the large clinical trial.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Gordis: In FY 1993, approximately 3 percent of applications received by NIAAA were submitted by Hispanic investigators. The Institute's overall success rate for FY 1993 was 19 percent, and the success rate for Hispanic investigators was 8 percent. Since NIAAA's number of awards is relatively small as compared to other NIH Institutes, and minor changes in numbers can reflect larger changes in rates, it is difficult to ascertain any factors that account for this difference.

SOCIAL AND BEHAVIORAL RESEARCH

Ms. DeLauro: How much overall funding does NIAAA devote to research on the behavioral and motivational aspects of alcohol abuse? Can you provide for the Committee that level of funding for the past 3 fiscal years, and what you plan to spend in FY '95? How will you work with the Office of Behavioral and Social Sciences, once that office is up and running -- will research funded through that office supplement rather than replace behavioral research you support?

Dr. Gordis: In FY 1993, NIAAA obligated $37.1 million for behavioral and social research. In FY 1994 and 1995, the Institute estimates that it will spend $39.7 million and $41.5 million, respectively.

NIAAA will provide any assistance requested by the new Office of Behavioral and Social Sciences Research (OBSSR) as it becomes established and expects to collaborate on the many issues regarding behavioral and social research. It is intended that funds from OBSSR will be used to supplement the research support provided by the NIH Institutes in this research area.

HEALTH SERVICES RESEARCH

Ms. DeLauro: The National Institute on Drug Abuse views research on drug abuse treatment and prevention services, the linkage between drug abuse and the primary health care system, and HIV/AIDS prevention services research as major components of its research program. I believe such research is critical. We must address a person's entire needs -- for example, day care for substance abusing mothers while they are in treatment -- if we are to be truly successful. You mentioned health services research in your testimony. Does your Institute attach a similar level of importance to health services research? What level of resources is devoted to health services research in the current fiscal year? How does that compare to FY '93, and what do you plan to spend in FY '95?

Dr. Gordis: Health Services Research is a very high priority in NIAAA. Included in our authorizing legislation is the provision that NIAAA spend 15 percent of our budget on this increasingly important research area. The objective of NIAAA's Health Services Research is to assess the effectiveness of preventive interventions in reducing alcohol-related problems and/or contributing risk factors. In addition to intervention studies, Health Services Research includes research on the financing, organization, management, enforcement, and utilization of prevention services and how they relate to the overall effectiveness of intervention.

In FY 1993, NIAAA spent $16.3 million on Health Services Research, and in FYs 1994 and 1995 will spend $27.8 million and $28.9 million, respectively.

ALCOHOL ABUSE IN WOMEN

Ms. DeLauro: Are there differences between men and women in the rate of alcohol abuse? Are you looking into why this may be so, both in terms of possible physiological differences, as well as behavioral, socioeconomic, familial or other factors? How much has been spent over the past 3 years on research into women and alcoholism, and how much do you anticipate spending in FY '94, and FY '95?

Dr. Gordis: Research on women's health is one of NIAAA's six major initiatives for which a Request for Application (RFA) was developed in FY 1993. Highlights of this RFA include examination of gender differences and identification of risk factors or markers that predict alcohol dependence and organ or tissue damage. An important area of NIAAA research, also highlighted in the recent RFA on Prevention, is alcohol and pregnancy, especially the study of Fetal Alcohol Syndrome.

Fewer women than men drink and, on the whole, women who drink consume less alcohol and have fewer alcohol-related problems than men. Yet, among the heaviest drinkers, women equal or surpass men in the number of problems that result from their drinking. The interval between onset of drinking-related problems and entry into treatment appears to be shorter for women. Women are known to be more susceptible to alcohol-induced liver damage than are men -- developing severe liver disease, especially alcoholic hepatitis and cirrhosis, with shorter durations of alcohol use and lower levels of consumption. There is mounting evidence that women who abuse alcohol also have a greater risk than men of developing cardiovascular disease, hemorrhagic stroke, and reproductive and endocrine anomalies. Institute-sponsored scientists will be expanding current research efforts directed at understanding alcohol's role in the genesis or exacerbation of these diseases, as well as investigating the mechanisms of this enhanced susceptibility. Studying the relative contribution of genetic factors compared to environmental factors in the development of alcohol dependence is a priority for NIAAA researchers.

NIAAA scientists are now exploring the link between alcohol consumption and breast cancer. This is an important initiative for 1995. Some epidemiologic studies have associated chronic alcohol consumption with an increase of about 10 percent in risk of breast cancer, especially for postmenopausal women. The risk appears to increase as the quantity and duration of alcohol consumption increases. However, other studies have found no evidence of such a link, suggesting that other factors, such as nutritional deficiency and genetic susceptibility, may be responsible for the increased risk. In addition, the Institute is supporting the largest and most in-depth longitudinal study of women's drinking ever conducted in the U.S. Data from this study will yield information on the antecedents, dynamics, and consequences of women's drinking. Analyses are providing information on indicators of the onset of problem drinking, environmental risk factors, and the influence of marital status. An important component of the study is to determine whether alcohol-related violence differs by gender and if women's drinking or alcohol-associated aggressive behavior may trigger their victimization.

Funding for women's health is $14,161,000 for FY 1992, $17,852,000 for FY 1993, $18,375,000 for FY 1994, and $21,630,000 for FY 1995.

WOMEN IN ALCOHOL RESEARCH

Ms. DeLauro: During last year's hearings, you noted that "increasing women investigators' involvement in alcohol research" was an important Institute goal. Can you tell us about your progress in achieving this goal? What efforts does your Institute make to attract additional funding applications from female researchers?

Dr. Gordis: NIAAA has a good track record for including women as principle investigators and advisors. For instance, our National Advisory Council is comprised of 12 members, six of whom are women. Out of 63 IRG members, 20 are women. The Board of Scientific Counselors, which advises our intramural program, has two women out of seven.

Ms. DeLauro: How many women and men researchers do you fund?

Dr. Gordis: In FY 1993, NIAAA supported 159 female principal investigators, and 303 male principal investigators.

Ms. DeLauro: Of the investigators receiving funding for the first time during the last year, what percentage are women?

Dr. Gordis: Of the new awards made in FY 1993, approximately 1/3 of the investigators are female.

Ms. DeLauro: What amount of funding is held by male researchers and female researchers?

Dr. Gordis: In FY 1993, $29,000,000 was awarded to female investigators, and $106,004,000 was awarded to male investigators.

TUESDAY, APRIL 26, 1994.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

NATIONAL INSTITUTE OF MENTAL HEALTH

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

NATIONAL INSTITUTE ON AGING

WITNESSES

HAROLD E. VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH
LAWRENCE, E. SHULMAN, M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
REX W. COWDRY, M.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH
JAMES B. SNOW, JR., M.D., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS
RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING
WILLIAM BELDON, DEPUTY ASSISTANT SECRETARY, BUDGET, OFFICE OF THE SECRETARY

Mr. SMITH. Okay. We will get started with the first panel today. Dr. Varmus is not here, but you can go ahead.

INTRODUCTION OF WITNESSES

Dr. SHULMAN. Yes, sir, Mr. Chairman.

Let me introduce the panel. To my right is Dr. James B. Snow, Jr., Director of the National Institute on Deafness and Other Communication Disorders. On my left is Dr. Rex W. Cowdry, the Acting Director of the National Institute of Mental Health; Dr. Richard Hodes, on my far left, is Director of the National Institute on Aging; and Mr. Beldon represents the Secretary's Office. I am the Director of NIAMS.

OPENING STATEMENT

Mr. Chairman, it is a privilege and pleasure to appear before you to discuss the many research programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases and to highlight some of our research accomplishments this year. This Institute has a large and diverse research agenda to address the numerous diseases that affect the joints, muscles, bones and the skin.

At some point in our lives, sir, nearly every American will be afflicted by one or more of these diseases. This year, Mr. Chairman, has been extraordinarily productive with major advances and discoveries in different fields.

NIAMS is only eight years old, but this has been our best year yet. Of highest priority for this Institute is research on osteoporosis, the leading cause of bone loss and bone fractures of the hips, spine and wrists.

Twenty-five million American women have osteoporosis. It is a women's disease four to one, and it is eminently preventable. We have had several developments this year as shown on Poster 1.

First, is an exciting report in January of the discovery of the gene that predicts bone density. This gene codes for the receptor for vitamin D. The gene identifies, early in life, those who are at risk for osteoporosis. This provides us with a new opportunity for prevention by ensuring that those at risk maximize calcium intake and exercise.

As you can see, Mr. Chairman, by the cover of the January 20th issue of "Nature," this is red-hot research.

Secondly, we have just launched a new B.O.N.E.S. initiative to further basic research on osteoporosis. We have forged a Federal working group, which I chair, on bone diseases to facilitate coordination, not only amongst the Institutes but amongst other agencies as well.

We also have a new national osteoporosis data group that is up and running. In September, we will begin funding a National Resource Center for Osteoporosis which will provide educational materials to the public.

On June 6th, 7th, and 8th, we will host an NIH consensus development conference on optimum calcium intake. Recent data has indicated that Americans' intake of calcium is much too low.

We have also made progress this year in the war against rheumatoid arthritis, the major crippler that causes red-hot, inflamed joints. This is also a women's disease three to one.

First, we recently had a report on the effectiveness of antibodies to TNF Alpha, a substance produced by immune cells that damages the joints. To date, improvement in arthritis patients has been impressive using this new approach. Other antibodies have been found that are shown to be effective, namely, antibodies as shown on the bottom right of poster 2 that block the formation of new blood vessels.

Another very high priority for this Institute is research on lupus, a life-threatening autoimmune disease that damages the kidneys, the joints and the skin. It is a disease of young women nine to one, especially African-American women three to one over white women.

In an exciting advance shown on Poster 3, scientists have just discovered a defective gene, the *fas* gene in a mouse model of lupus. Replacing this with a normal *fas* gene prevents the kidney damage that usually occurs in these lupus mice.

How this works is just fascinating. There is a process of programmed cell death called "apoptosis" that normally eliminates damaged immune cells. This process is under the control of this *fas* gene. When this gene is defective, harmful cells survive, causing the autoimmune damage of lupus.

The next step is to determine if such an abnormality exists in women with lupus. And it has just been reported in the March 25th issue of "Science," that 6 of 10 patients with lupus, carry the *fas* gene

The past year has also brought a very important breakthrough in our research on the causes of spinal arthritis, a young men's disease. Three years ago, I reported to this Committee the remarkable discovery in which a human gene, HLA-B27, that is found in over 90 percent of patients with spinal arthritis, was injected into rats. These transgenic rats developed not only arthritis of the spine and joints, but also gut inflammation, and skin and nail changes of psoriasis. All of these conditions are associated with spinal arthritis (poster 4). The conclusion then was that HLA–B27 caused these diseases. The same experiment was repeated with such transgenic rats bred in a germ-free environment. They still developed the skin and nail changes, as you can see from the chart, but they did not develop the arthritis or gut inflammation. The conclusion now is that the gene alone can't cause the arthritis, an infectious agent must also be present. The challenge now is to find the bug.

NIAMS continues to support productive research on many serious rare diseases, including both inherited and acquired connective tissue diseases listed on poster 5. We have made critical genetic discoveries in many of them. These include the very serious and devastating skin diseases, such as epidermolysis bullosa. Ichthyoses and scleroderma, and life-threatening heritable connective tissue diseases, as listed here. We have recently issued a new announcement for support on research registries as requested.

Finally, basic research is critical to the mission of NIAMS. One of the most spectacular discoveries this year has been in basic muscle research (Poster 6). After 10 years of research scientists have discovered the 3-D structure of a main muscle protein called myosin.

They then went on to work out the interaction between myosin and the other main muscle protein, actin. They have been able to describe, in molecular terms, the structural basis of how chemical energy produces force and motion. This discovery was featured in the July 2nd issue of "Science," as I show you here.

As you can see, the various programs of NIAMS are generating many promising research advances and discoveries. Scientific opportunities abound. Our budget request for FY 1995 is $228,413,000.

I will be happy to respond to your questions.

[The prepared statement and biography of Dr. Lawrence Shulman follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Mr. Chairman, members of the committee, it is a great privilege and pleasure to appear before you once again to discuss the many research programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and to highlight some of our research accomplishments this past year.

NIAMS has a large, complex research agenda. It encompasses a broad array of diseases that affect the very components of the body that shape our form and structure, and enable us to move. All together, these diseases of the joints, muscles, bones, connective tissue, and skin will afflict nearly every American at some point in their lifetime. Moreover, these diseases affect people of all ages, race, and color. Some of these disproportionately affect special populations, such as women, minorities, children, or the elderly. The NIAMS is dedicated to lessening the burden imposed by these diseases. I am pleased to report to you that we have seen promising advances in several areas.

Osteoporosis is an eminently preventable disease that results from porous bone that easily fractures. At least 25 million American women suffer from osteoporosis. It is the major underlying cause of bone fractures in both postmenopausal women and the elderly. Researchers have recently found a gene that can predict bone density. This landmark discovery will make it possible to identify, early in life, individuals at high risk for osteoporosis and to initiate prevention programs. One way to build bone--and thus prevent osteoporosis--is to take in enough calcium. With this in mind, the NIAMS is sponsoring a Consensus Development Conference this year to establish guidelines for optimum levels of calcium intake for people of different ages.

Another high priority for our Institute is research on the many forms of arthritis. We are making much progress in this field, including research on diseases such as lupus, rheumatoid arthritis, scleroderma, and fibromyalgia that largely affect women. Recent research has uncovered clues to explain why rheumatoid arthritis, a major crippling disease, improves greatly in three-fourths of patients during pregnancy. The discovery indicates that genetic differences between mother and child promote immune reactions that combat the arthritis. These findings offer a new avenue of research into the mechanisms of remission in rheumatoid arthritis, and thus, may lead to new treatment strategies.

There has been much discussion, over the years, on the possible benefit of the antibiotic minocycline in treating rheumatoid arthritis. The NIAMS has recently completed a large multicenter clinical study on minocycline in rheumatoid arthritis; it found that this agent has some benefit and low toxicity in treating the arthritis. Because it remains unclear how minocycline works, NIAMS is convening a group of scientists to explore the results of the trial.

I would like to share with you now the progress we are making with lupus, a serious disease that disproportionately affects women, especially African-American women. In recent initiatives, the NIAMS is now supporting new basic research on the molecular causes of lupus, and basic and clinical research on why lupus is more prevalent in certain populations. In one of the exciting new advances in lupus research, scientists have just discovered that replacing a single defective gene can prevent lupus tissue injury and reduce autoantibodies in a mouse model of lupus. This gene, called the *fas* gene, normally enables the body to eliminate damaged or harmful cells, such as those that cause tissue damage in lupus. In the mouse model, researchers replaced the flawed gene, and the mice no longer developed signs of lupus. This remarkable research may open the door to new treatments for women with lupus.

To increase research on arthritis in children, the NIAMS organized a highly productive scientific workshop this year. This workshop covered basic and clinical research for several rheumatic diseases of children. Based on the published proceedings, the Institute will actively encourage new research in areas recommended by the leaders in this field. Also this year, the NIAMS funded an Exploratory Research Center in Juvenile Rheumatic Diseases where investigators will study the genetics and other aspects of these diseases.

A very important breakthrough occurred this year in research on the causes of spinal arthritis. You may recall that three years ago I reported to you a remarkable discovery in which a human gene, HLA-B27, that is found in over 90 percent of patients with spinal arthritis, was injected into rats. These transgenic rats developed not only arthritis of the spine and joints, but also skin and nail lesions of psoriasis and Reiter's disease, both associated with spinal arthritis. This research indicated that genetics plays an essential role in causing these diseases. The same study has now been repeated using HLA-B27 transgenic rats that have been bred in a completely germ-free environment. Remarkably, although the germ-free rats still developed the skin and nail changes, they did not develop the arthritis that was observed in animals raised in a normal environment. This research proves that the HLA-B27 gene alone cannot induce the arthritis--an infectious agent must also be present. The challenges now are to identify the responsible infectious agent and to find the link between it and the gene.

Another important new advance this year is a new highly sensitive test, using modern techniques of the polymerase chain reaction, to detect Lyme disease bacteria in the joint fluids of patients with arthritis caused by Lyme disease. This test will greatly aid in the diagnosis and treatment of Lyme arthritis by making it possible to accurately determine when bacteria is the cause of the chronic arthritis, and when it is not.

Osteoarthritis is the most common form of arthritis, affecting an estimated 16 million Americans. In a recent study in an animal model of osteoarthritis, scientists have shown that the antibiotic doxycycline prevented the development of the arthritis because of the ability of doxycycline to block collagenase, an enzyme that degrades cartilage. To encourage more research on this common and disabling disease, NIAMS is sponsoring a workshop on "New Horizons in Osteoarthritis," and a Consensus Development Conference on Total Joint Replacement.

NIAMS continues to support research on both inherited and acquired connective tissue diseases, such as osteogenesis imperfecta, Marfan syndrome, Ehlers-Danlos syndrome, and scleroderma, and will hold a workshop in the fall to build on recent scientific advances. Recent discoveries in osteogenesis imperfecta--or "brittle bone disease"--include a new mouse model of the disease. Scientists have also discovered that the weakness of bone in this disease is due more to abnormal crystallization of bone than to defective collagen production.

Research on all diseases of bone is important to the NIAMS. To facilitate and enhance knowledge and understanding of bone diseases, the Institute will award a grant to establish an Information Resource Center on Osteoporosis, Paget's Disease, and Related Bone Disorders.

Basic research is critical to the mission of the NIAMS. One of the Institute's greatest advances this year occurred in fundamental muscle research when scientists discovered the 3-dimensional structure of the main protein of muscle. This exciting discovery reveals with precision how the molecules in muscle use chemical energy to produce force and motion.

Much progress has also been made in the last several years in research on the genetic causes of inherited skin diseases, such as epidermolysis bullosa. Exciting advances at the molecular level are providing insights into the underlying causes of many of these skin diseases.

This year, the NIAMS issued a request for applications to establish research registries for rare diseases, including skin diseases such as the ichthyoses. The Institute will also support two additional Research Core Centers for Skin Diseases to reach its goal of six centers.

As a followup to a previous workshop, NIAMS will sponsor a scientific workshop on alopecia areata to provide for further exchange of information and to stimulate more research on the disease.

We continue to be extremely proud of the research being conducted in our Intramural Program. Scientists are making exceptional progress in research on the inherited rheumatic disease, familial Mediterranean fever (FMF). They have localized the genetic defect for FMF to the short arm of chromosome 16, and they are now collaborating with investigators at the National Center for Human Genome Research to focus in on the specific gene. Two new enzyme deficiencies causing muscle-weakening disease have been discovered. The genetics of immune-mediated inflammation is being actively investigated.

As you can see, Mr. Chairman, the programs of the NIAMS are many, and research opportunities abound. To continue our research efforts, we are requesting an FY 1995 budget for the NIAMS of $228,413,000. I will be pleased to answer any questions you may have.

SHULMAN, DR. LAWRENCE E.
Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

July 25, 1919, Boston, Massachusetts

Education: Harvard University, A.B., 1941; Yale University Graduate School, Ph.D., 1945; Yale University School of Medicine, M.D., 1949.

Professional History: 1949-50, Intern, Medicine, The Johns Hopkins Hospital, Baltimore, Maryland. 1950-51, Ayerst, McKenna and Harrison Fellow in Endocrinology, The Johns Hopkins University School of Medicine. 1951-52, Vernon D. Lynch Fellow in Internal Medicine, The Johns Hopkins University School of Medicine. 1952-53, Assistant Resident, The Johns Hopkins Hospital. 1954-present, Physician, The Johns Hopkins Hospital. 1955-75, Director, Connective Tissue Division, Department of Medicine, The Johns Hopkins University School of Medicine. 1960-66, Physician-in-Charge, Arthritis Clinic, The Johns Hopkins Hospital. 1956-67, Physician-in-Charge, Connective Tissue Clinic, The Johns Hopkins Hospital. 1966-69, Physician-in-Chief, Division of Chronic and Community Medicine, The Baltimore City Hospitals, Baltimore, Maryland. 1970-73, Associate Professor of Medical Care and Hospitals, The Johns Hopkins University School of Hygiene and Public Health. 1964-present, Associate Professor of Medicine, The Johns Hopkins University School of Medicine. 1976-80, Acting Associate Director for Arthritis, Musculoskeletal, and Skin Diseases, National Institute of Arthritis, Metabolism, and Digestive Diseases. 1980-83, Associate Director, Arthritis, Musculoskeletal and Skin Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. 1983-1986, Director, Division of Arthritis, Musculoskeletal, and Skin Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. 1986, Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases. 1987-present, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Professional Organizations: American Association for the Advancement of Science, American College of Physicians, American Federation for Clinical Research, American Rheumatism Association (President, 1974-75), American Society for Bone and Mineral Research, The Arthritis Foundation, Brazilian Society of Rheumatology, Carla Curzio Neapolitan Society, Lupus Foundation of America, New York Academy of Science, Pan American League Against Rheumatism (President, 1982-86), Society for Clinical Trials, Sydenham Society, Society for Investigative Dermatology.

Honors, Awards: Senior Investigator Award, The Arthritis Foundation, 1957-62. Pemberton Memorial Lecture, 1963. Fellow, American College of Physicians, 1967. Wallace R. Graham Memorial Lecture, Toronto, 1973. The Heberden Medal for Research in the Rheumatic Diseases, Heberden Society, London, 1975. Distinguished

Service Award, The Arthritis Foundation, 1979. Honorary Member, Brazilian Society of Rheumatology, 1980. Honorary Member, Chilean Society of Rheumatology, 1981. Knowles Lecture, San Francisco, 1982. Honorary Member, Costa Rican Association of Rheumatology, 1984. Honorary Member, Australian Rheumatism Association, 1985. The Public Health Service Superior Service Award, 1985. National Lupus Hall of Fame, 1986. Honorary Member, Swiss Society of Rheumatology, 1987. Elected Master, American Rheumatism Association, 1987.

Consultation on Research on Osteoporosis, World Health Organization, Geneva, 1988. Chairman, Scientific Group on the Rheumatic Diseases, World Health Organization, Geneva, 1989. Special Award of Gratitude, Coalition for Heritable Connective Tissue Diseases, 1990. Special Recognition Award, National Osteoporosis Foundation, 1991. Award for Leadership in Promoting Orthopaedic Research, American Academy of Orthopaedic Surgeons, 1992. Presidential Citation for leadership in biomedical research from the American Academy of Dermatology, 1993.

Osteoporosis

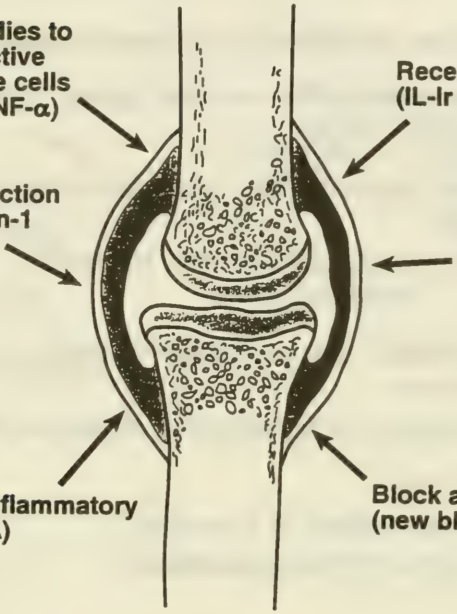
New Developments

- Gene discovered; predicts bone density
- "BONES" Initiative: new basic research
- Federal Working Group on Bone Diseases
- National Osteoporosis Data Group
- National Resource Center for Bone Diseases
- Consensus Development Conference: Optimal Calcium Intake

POSTER 1

Rheumatoid Arthritis

New Ways To Attack It



Antibodies to destructive immune cells (Anti-TNF-α)

Block production of interleukin-1 (TENIDAP)

Novel anti-inflammatory agent (NOVA)

Receptor blockers (IL-Ir antagonist)

Inhibitors of destructive enzymes

Block angiogenesis (new blood vessels)

POSTER 2

Lupus (SLE)

Major Advance

- Defective *fas* gene in mouse model of SLE
- Replacement with normal gene prevents lupus in mice
- Impaired apoptosis: programmed cell death
  - — normally eliminates harmful immune cells
- Gene defect allows harmful cells to survive
  - — causes autoimmune disease (SLE)
- Next steps:
  - — find defect in humans
  - — correct therapeutically

POSTER 3

Spinal Arthritis Group

Transgenic Rats - Human HLA-B27 Gene

	Environment	
	Normal	Germ-Free
Spinal arthritis	+	–
Other arthritis	+	–
Gut inflammation	+	–
Psoriasis	+	+
Nail changes (Reiter's)	+	+

POSTER 4

Rare Diseases

Connective Tissue Diseases

- Epidermolysis Bullosa (EB)
- Ichthyosis
- Marfan's Syndrome
- Ehlers-Danlos Syndrome
- Scleroderma
- Osteogenesis Imperfecta
- Duchenne's Muscular Dystrophy
- Familial Mediterranean Fever

- New Announcement for Research Registries

POSTER 5

Basic Muscle Research

Major Discovery

- 3-D structure of main muscle protein (myosin)
- Myosin-actin interactions
- Molecular motor of muscle motion
- How chemical energy produces
    - — force
    - — motion

POSTER 6

Ms. PELOSI [presiding]. Thank you very much Dr. Shulman.

We are going to hear from Dr. Cowdry from the National Institute of Mental Health next.

Welcome.

Dr. COWDRY. Thank you, Ms. Pelosi. It is indeed an honor to appear before you today to present the appropriations request for the National Institute of Mental Health.

This is actually my first action as the Acting Director of NIMH and I am delighted to be here.

Ms. PELOSI. Welcome. Congratulations.

Dr. VARMUS. First day.

OPENING STATEMENT

Dr. COWDRY. I would like to take note of Dr. Goodwin's 29 years of Federal service, his distinguished career, his many contributions to our understanding of mental illness and its treatments, and his service to the mentally ill whom we serve as an Institute.

My opening remarks can be summarized in four statements: Mental illnesses are real; mental illnesses are prevalent; they are costly to society; and research is a vital part of the answer.

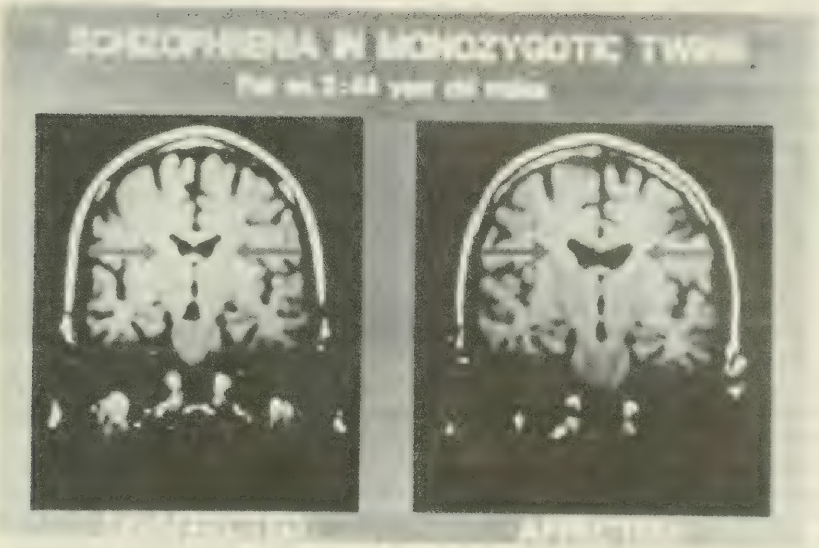
Mental illnesses are real. For one kind of evidence of the reality of mental illness, I would invite you to make a visit to the NIMH Neuropsychiatric Research Hospital and spend an hour talking with our research participants. Or you might ask, if you could, Ernest Hemingway or Sylvia Plath or more recently, Kurt Cobain or Vincent Foster or John Wilson, or any of the over 30,000 Americans each year who found mental illness, often coupled with substance abuse, not only to be real and painful, but also a fatal illness as described in this last week's article in "Newsweek." An excellent article.

Or read in the same issue of "Newsweek" a brief account of his own depression by William Styron—one of the most eloquent, vivid and painful brief descriptions I have ever read.

Mental illness is not the result of a lack of willpower or of fortitude. Indeed, it requires great strength to deal with mental illness when the main tool that most of us use to cope—our minds—is itself impaired.

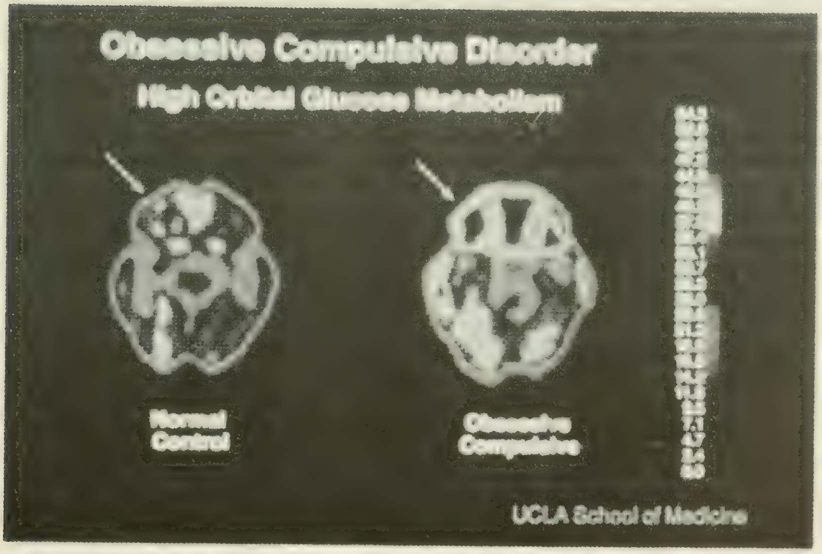
NIMH-supported research provides further evidence for the reality of mental illness. The Institute's genetic studies provides one kind of hard evidence for a biological underpinning for mental illness. Brain imaging studies, such as you see here, provide another kind of hard and visible evidence.

[Chart follows:]



SCHIZOPHRENIA IN MONOZYGOTIC TWINS

Pair no. 2 : 44 year old males



Obsessive Compulsive Disorder

High Orbital Glucose Metabolism

UCLA School of Medicine

Dr. COWDRY. Research studies demonstrate abnormalities in brain neurotransmitters. Clinical trials demonstrate that biological, behavioral and other psychotherapeutic treatments provide effective treatment for many disorders.

I would refer any remaining skeptics to Congress' own Office of Technology Assessment report on the Biology of Mental Disorder.

Mental illnesses are prevalent. In the course of a year, 9 percent of Americans have a diagnosable episode of mental illness producing disability; in the course of a lifetime, one in four. If we ask people in this room, most of us would know a relative or a friend who has had episodes of mental illness.

My own relatives have suffered from depression. In earlier generations before the advent of effective treatment there have been at least two suicides.

For relatives fortunate to have lived in our age following the development of effective pharmacotherapy and other therapies, treatment with antidepressants has produced remarkable results.

Mental illnesses are costly to society. Health services research funded by the NIMH conservatively estimates the annual direct and indirect costs of mental illness at $148 billion, second only to cardiovascular diseases in their effect.

Severe mental illnesses account for 25 percent of all Federal disability payments.

In the last 30 years, we have come a remarkable distance in understanding these illnesses and developing treatments and reducing stigma, but much remains to be done—and research is vital.

You might ask, what are the recent fruits of this NIMH funded research?

Suicide in older men, a group with the highest rate of suicide, is almost always related to the presence of a treatable depression. This mirrors earlier findings that suicide in adolescents and younger adults is closely associated with treatable mental illness. Antidepressants, long known to be effective treatments for severe major depression, have been found to help in the treatment of a form of chronic depression known as dysthymia.

Manic-depressive illness across generations shows a phenomenon referred to as "anticipation," that is, the illness in the family tends to occur earlier and be more severe in succeeding generations. There are other major medical illnesses where this phenomenon is associated with a specific DNA abnormality, trinucleotide repeats. The search for an abnormality in manic-depressive illness is underway.

Treatment of schizophrenia with clozapine, our most expensive antipsychotic agent, is nonetheless cost-effective. Outpatient treatment of schizophrenia with intensive structured community intervention dramatically reduces the rate of rehospitalization and therefore is cost-effective.

Panic disorder and agoraphobia can be effectively treated with a structured program of cognitive behavioral therapy.

Congress requested a report from the National Advisory Mental Council on Health Care Reform for Americans with Severe Mental Illnesses: schizophrenia, depression, manic depressive illness, obsessive-compulsive disorder, panic disorder, and childhood mental illnesses. This report, based on our NIMH services research, demonstrates that equitable coverage for severe mental illness, coverage on a par with other medical illnesses, is cost-effective, producing net savings to our society.

In the absence of an effective treatment or vaccine for AIDS, behavior change is the only way of reducing the toll that this illness takes on our society. Controlled studies show that specific cost-effective interventions with community opinion leaders, for example, can reduce high-risk behavior in the community by 22 to 36 percent, compared with a no intervention comparison community. Similar programs of intervention with runaway youths in New York show similar ability to change high-risk behavior.

I have received the yellow warning card from Mr. Fitzsimmons.

Let me describe to you in closing the Human Brain Project. Each of us has our own information superhighway within our own head: The billions of neurons comprising the human brain. This information superhighway is even more remarkable than the global information superhighway. It can not only retrieve information from remote sites in the brain and synthesize facts, it can also have feelings, direct behavior and create, in short, this information superhighway that we have is human.

One essential task of neuroscience research is to understand and map the vital features of this superhighway. The Human Brain Project will build a visible database of information about the brain, organizing and integrating it in a way that enables researchers to readily retrieve information from existing research, to develop new ideas about how this miraculous and complex organ operates and to build these ideas into new approaches to mental and neurological illnesses.

To continue these and other research efforts, NIMH requests $637.9 million in fiscal year 1995.

Thank you.

[The prepared statement and biography of Dr. Rex Cowdry follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Acting Deputy Director
National Institute of Mental Health

It is my pleasure to appear before you to discuss the research efforts of the National Institute of Mental Health (NIMH) and, in particular, to report on our progress in addressing the priorities recommended by Congress and our Advisory Council.

Before I begin, Mr. Chairman, let me note that I am delivering this statement not only for NIMH, but also for the Institute Director, Dr. Frederick K. Goodwin, who will soon be leaving the Institute to establish a Center on Science, Medicine, and Human Values. In addition to recognizing Dr. Goodwin's distinguished 29-year career in research and mental health leadership, it is a special pleasure to note that he was my original research mentor when I came to NIMH 17 years ago. The field, and persons with mental illness, are enormously grateful for Dr. Goodwin's many contributions.

The President's fiscal year 1995 budget request for the NIMH responds to urgent needs to address the causes, treatment and prevention of mental illnesses which, in any given year, affect one-fifth of the population and produce substantial disability in half of those affected. From individual to society, from infancy to old age, mental illness confounds, disables, and impoverishes patients and their families alike. It is also very costly to our Nation, with direct and indirect costs estimated at $148 billion per year, including 25 percent of all Federal disability payments. Yet, as research has shown, mental illnesses are definable; they are increasingly treatable in a cost-effective manner; and some are preventable.

These advances are exciting for those of us whose lives have been devoted to unlocking the mysteries of the brain. They are equally exciting for those of us who each day treat the unique suffering associated with mental illness. But they are most exciting for those of us who are directly affected by mental illnesses -- my own extended family has been visited by major depressions and by suicide.

A scientific focus on understanding, treating, and preventing mental disorders is the defining mission of the NIMH. As our Nation enters the second half of the Decade of the Brain, NIMH's scientific accomplishments already have begun to develop a new level of understanding of the brain and behavior--understanding that is being applied to alleviate human suffering. Neuroscience, an area of interdisciplinary research focused on how specific brain functions (or dysfunctions) relate to particular behaviors, has made remarkable advances in exploring the human brain. Behavioral research has made substantial progress exploring the factors which shape our interactions with the world, and has demonstrated an ability to improve the lives of many of our citizens. In particular, it has demonstrated an ability to change behaviors that put some of our citizens at increased risk for developing AIDS. Psychopharmacologic research has advanced our understanding of the effects of drugs and their role in treating mental illnesses. And a concerted effort in the area of services research is improving our ability to reach those who need treatment for mental illnesses and to do so in the most effective and cost-effective manner.

To illustrate the breadth of the Institute's efforts in understanding mental illnesses, efforts spanning basic neuroscience, clinical pathophysiology, and treatment efficacy and effectiveness studies, I would like to focus my remarks primarily on new findings from NIMH-funded research on schizophrenia, the most chronic and disabling of the severe mental disorders and one of the most formidable challenges to psychiatric science. Typically, the major symptoms of schizophrenia appear in late adolescence or early adulthood. These include both the "positive" symptoms of hallucinations, delusions, and bizarre thought patterns that typically lead to psychiatric treatment and hospitalization, and the "negative" symptoms of social isolation and withdrawal. The illness tends to first appear just as adult life begins, shattering career plans, ending relationships, and tormenting those directly affected and their families and friends. More than 2 million Americans have schizophrenia in any given year.

Today, I am able to report that an increasing number of investigations point with remarkable consistency to the likelihood that schizophrenia is the manifestation of an abnormality in brain development. Strong evidence for such an abnormality is found in studies of post-mortem tissue of brains from individuals with schizophrenia. Investigators working at an NIMH-supported Center for Neuroscience and Schizophrenia have found that particular populations of neurons normally found in the outer layers of the prefrontal cortex were concentrated instead in deeper layers of the cortex on patients with schizophrenia, suggesting that these neurons had not completed their migration during brain development and may not have made the appropriate connections between the prefrontal cortex and the rest of brain. This developmental abnormality corresponds anatomically to previous reports of reduced activity in the prefrontal cortex in schizophrenia demonstrated by brain imaging.

One of the enduring puzzles of schizophrenia is the appearance of the disease long after the presumed developmental injury. Intramural researchers have now developed a novel animal model in which very early injury to one part of the brain, the hippocampus, produces behavioral abnormalities which are only evident when the animal approaches adulthood. These behaviors correspond to behavioral abnormalities produced by adult lesions in prefrontal cortex and elicited by the release of the neurotransmitter dopamine.

Dopamine is the neurotransmitter most closely linked to schizophrenia. Neuroscience researchers have successfully cloned, sequenced, identified, and localized five different receptors for dopamine and now have demonstrated that one of these--the D4 receptor--is elevated in specific brain regions in schizophrenia. A further link in this chain is forged by the findings that both clozapine and risperidone, recently introduced second-generation antipsychotic drugs which appear to have particular efficacy against the "negative" symptoms of schizophrenia, are particularly active in blocking this D4 receptor site.

Clinical research shows that these new antipsychotic medications enhance the accessibility of once-intractable patients to community-based treatments. Complementing research on medication efficacy are new services research studies on treatment effectiveness. For example, the NIMH-funded "Assertive Community Treatment" model, a managed care approach to providing severely disabled patients with intensive outpatient treatment, has demonstrated new models of treatment can be effective and at the same time substantially reduce treatment costs.

These findings from our schizophrenia research program represent a small part of our ongoing efforts recommended by the National Plan for Research in Schizophrenia and by the Decade of the Brain report. Similar illustrations of research efforts exist for other serious mental illnesses, including mood disorders, anxiety disorders, eating disorders, disorders of childhood, and obsessive-compulsive disorder. Rather than catalog these advances, I would like to describe briefly our efforts in other priority areas.

Mental health services research is a high NIMH priority, given the urgent need for reliable data about the effectiveness and cost-effectiveness of treatments for mental disorders in a variety of mental health service systems. This year, our investment in services research will reach 15 percent of our appropriated funds. We anticipate that this research will help inform discussions of mental health services and benefits as we reform our system of health care.

Research on child and adolescent mental disorders are also an NIMH priority. While much scientific effort is being directed at the severe disorders experienced by children, our research also is concerned with the causes, treatment, and prevention of childhood behavior problems. A recent contribution of NIMH researchers has been the utilization of sophisticated behavioral tests that can be administered to infants as young as six months who suffer from the genetic disorder phenylketonuria (PKU). Though the disorder can be treated by dietary restriction of phenylalanine, the NIMH research has shown that even the "acceptable" level of phenylalanine in blood may cause significant cognitive deficits, and suggests that blood level guidelines should be reassessed.

In conjunction with the Board of Scientific Counselors of the NIMH Intramural Research Program, we are conducting an in-depth evaluation of that program. Our aim is to ensure that the Intramural program makes optimal use of the funding it receives and retains its reputation for innovation and leadership earned over the past 45 years.

Our budget reflects a unique convergence of public health needs, basic scientific data, and evolving clinical insights. To continue the scientific research activities highlighted here, and others, we request $545,223,000.

I will be pleased to answer any questions.

CURRICULUM VITAE
REX WILLIAM COWDRY, M.D.

EDUCATION:

1968:	A.B.	- Yale College, (Psychology)
1973:	M.D.	- Harvard Medical School
1973:	M.P.H.	- Harvard School of Public Health

LICENSED to practice Medicine, District of Columbia (1978-), Commonwealth of Virginia (1977-).

PROFESSIONAL EXPERIENCE:

1973-1976:	Resident in Psychiatry, Massachusetts Mental Health Center, Boston
1975-1976:	Consultant, Washingtonian Center for the Addictions, Boston
1977-1978:	Consultant, Mount Vernon Center for Community Mental Health, Alexandria, VA
1977-1981:	Personal Psychoanalysis
1977- -- :	Private practice (part-time)
1978- -- :	Department of Psychiatry, Georgetown University School of Medicine Assistant Professor of Psychiatry (1978-1979) Assistant Clinical Professor of Psychiatry (1979-1983) Associate Clinical Professor of Psychiatry (1983-present)
1976- -- :	Intramural Research Program, National Institute of Mental Health (NIMH) Staff Psychiatrist (1976-1982) Chief, Outpatient Depression Studies (1978-1981) Chief, Borderline Personality Disorders Study (1982-1987) Associate Clinical Director for Outpatient Studies (1982-1983) Clinical Director (1984-1987)
1984-1987:	Medical Board, The Warren Grant Magnusen Clinical Center, NIH Chairman, Budget Committee (1985-1986) Chairman of the Medical Board (1986-87)
1986-1988:	Acting Deputy Director, NIMH
1987- -- :	Chief Executive Officer, Neuropsychiatric Research Hospital, Intramural Research Program, NIMH
1994- -- :	Acting Deputy Director, NIMH

FELLOWSHIPS AND AWARDS:

American Field Service School Program Scholarship (1963-1964)
United States Presidential Scholar (1964)
National Science Foundation Summer Research Associate, Yale University (1967, 1968)
United States Public Health Service Fellowship, Faculty of Medicine, University of Belgrade, Yugoslavia (1972)
Kennedy Fellow, Interfaculty Program in Medical Ethics, Harvard University (1973)
Falk Fellow, American Psychiatric Association (1974-1976)
Administrator's Award for Meritorious Achievement, Alcohol, Drug Abuse, and Mental Health Administration (1985, 1988)
Fellow, American Psychiatric Association (1990)
Exemplary Psychiatrist Award, National Alliance for the Mentally Ill (1992)

OTHER ACADEMIC AND PROFESSIONAL ACTIVITIES:

Teaching Experience

Instructor in Psychiatry, Harvard Medical School (1973-1976), (Biostatistics and Psychopharmacology)
Chief Resident, Service I, Massachusetts Mental Health Center (1975-1976), Clinical and administrative supervision
Intramural Research Program, NIMH (1976- --), Supervision and seminars for psychiatric residents and fellows; Director of Residency Training (1984-1987)
Georgetown University School of Medicine (1978-1979), Supervision of individual psychotherapy, seminars in psychopharmacology, case conferences
George Washington University School of Medicine (1989-1991), Supervision of psychiatric evaluation and treatment

Appointments:

American Psychiatric Association (1974-present)
  (1974-76), Committee on Peer Review
  (1979-81), Committee on the Protection of Human Subjects
  (1983-85), Task Force on the Effects of Lithium on the Kidney
ADAMHA Task Force on Regulations Concerning Research Involving the Institutionalized Mentally Disabled (1979-81)

Ms. PELOSI. Thank you very much.

The committee notes your comments about Dr. Goodwin and joins you in commending him for his years of service and enabling you, in fact, to be here today at this point and making a very excellent presentation.

Next, we will hear from Dr. Snow.

OPENING STATEMENT

Dr. SNOW. Thank you, Madam Chairwoman. It is a pleasure to appear before the Committee to discuss the progress and programs of the National Institute on Deafness and Other Communication Disorders.

The NIDCD supports research that will benefit 46 million Americans that are challenged by communication disorders and will provide new basic knowledge about the processes of human communication.

Five years ago when the NIDCD was created, only a few genes causing deafness had been found and those genes were in the disease process in which deafness was only part of the problem. Now more than 20 genes causing hearing impairment have been found.

Among recent discoveries are an autosomal dominant gene, a mitochondrial gene and an X-linked dominant gene found by NIDCD intramural scientists. The next step in the study of hereditary hearing impairment will be to determine the structural and functional roles of genes expressed throughout the auditory system.

The difficulty in understanding conversation in background noise is the major problem in the use of hearing aids, and the collaboration of the NIDCD with the Department of the Veterans Affairs addresses this problem. This five-part collaboration, consisting of research project grants, contracts, clinical trials and biennial conferences, should provide tangible benefit to the 20 million Americans who could benefit from an improved hearing aid.

The NIDCD is supporting a number of studies on the regeneration of sensory cells. Most recently investigators have demonstrated hair cell regeneration in cultures of human inner-ear tissue. This first breakthrough in human hair cell regeneration must be exploited quickly for the benefit of millions of hearing-impaired Americans.

Similarly, Institute-supported studies of smell and tastes sensory cell regeneration may play a major role in research of the therapeutic repair of the central nervous system. Recent studies conducted by NIDCD-supported scientists of children with Williams syndrome, a disorder in which children are mentally challenged and language delayed, have brought into question the tenet that language is constrained or paced by cognitive skills. These studies are expanding our understanding of brain and behavior relations.

The NIDCD expends 83 percent of its budget on extramural grants; 3.2 percent on training; 3.5 percent on research and development contracts, principally of cochlear implants and hearing aids; 5.7 percent on intramural research; and 4.4 percent on research management and support.

As areas of opportunity for extraordinary progress become apparent, they are supported through research project grants ordinarily since there is usually sufficient investigator initiative. An example is sensory cell regeneration. If there is not sufficient initiative, a decision is made by the staff and by the appropriate external advisory group to stimulate activity in the extramural research community through program announcements and requests for proposals, or if stronger direction is required, through requests for proposals for contracts, as in the development of new speech processing strategies and devices for cochlear implants and hearing aids.

For its intramural research program, the NIDCD chooses areas of emphasis in which the state of the science lend itself to rapid progress, there is inadequate activity in the extramural community and the payoff will benefit large numbers of people. For these reasons, the NIDCD Intramural Research Program is emphasizing molecular genetics of hearing impairment and development of vaccines against otitis medea.

The NIDCD has started its Partnership Program, a comprehensive minority research and training demonstration project with four academic centers which have large enrollments of minority persons underrepresented in biomedical and behavioral research. This program will exchange students, scientists, and administrators and maximize the opportunities to participate in fundamental and clinical research.

Now, that the NIDCD is five years old, there is a steady flow of important research findings in each of the seven program areas. NIDCD support has stimulated research training in basic laboratories and clinical settings. The NIDCD's fifth anniversary ceremony was a moving celebration of science. Investigators presented the newest and the best science and, importantly, gave force and direction for the future.

The NIDCD is fulfilling a promise to improve life for all Americans who have or will be challenged by disorders of hearing, balance, smell, taste, voice, speech, or language.

Madam Chairperson, the 1995 budget request is $167.129 million.

I would be pleased to try to answer any questions that you have.

[The prepared statement and biography of Dr. James Snow follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute on Deafness and Other Communication Disorders

It is a pleasure to appear before this committee to discuss the programs and progress of the National Institute on Deafness and Other Communication Disorders (NIDCD). The NIDCD supports research that will benefit the 46 million Americans challenged by communication disorders and provide basic new knowledge about the normal processes of human communication.

Five years ago, when the NIDCD was just beginning to support research as a new institute, only a few genes causing deafness had been found and those were genes discovered in diseases in which deafness was only a part of the problem. Now, more than twenty genes for hereditary hearing impairment have been found. Some of these cause syndromes which include identifying features in addition to deafness. Nonsyndromic hearing impairment, on the other hand, is the most prevalent form of hereditary hearing impairment throughout the world, and now several nonsyndromic deafness genes have been found. Among these are an autosomal dominant gene found by NIDCD funded extramural scientists, a mitochondrial gene found by an extramural team, and an X-linked, dominant gene found by NIDCD intramural scientists. The X chromosome gene is near the gene responsible for Duchenne muscular dystrophy(DMD). NIDCD intramural scientists are trying to determine if the DMD gene product, dystrophin, is expressed in the inner ear. The next step in the study of hereditary hearing impairment will be to determine the structural and functional roles of the genes expressed throughout the auditory system.

For several decades, there has been great concern about the need to improve hearing aid technology, especially to develop aids that would permit the understanding of conversation in noisy environments. The NIDCD and the Department of Veterans Affairs have developed a five-part collaboration designed to yield a comprehensive approach to this long-standing problem as well as address many other hearing aid issues and to offer tangible help to the 20 million Americans who could benefit from improved hearing aids. These initiatives encourage basic research on the effects of signal processing and ways to measure the benefit of amplification for hearing-impaired persons and the development of a program for design and evaluation of new and existing strategies and technologies. Much needed clinical trials are scheduled to begin in FY 1995. Also we will hold the first biennial interdisciplinary forum on hearing aid research and development in 1995. By identifying the appropriate resources, forging strong collaborations, and fostering innovation, we believe these initiatives demonstrate a responsible and cost-efficient way to apply basic and clinical research to a major problem.

Progress in other areas has created outstanding opportunities for further research. Clinical application of molecular and cellular biology to the problem of the loss of auditory and vestibular hair cells caused by commonly administered, lifesaving antibiotics has yielded a strategy to minimize or prevent ototoxicity.

The NIDCD places a high priority on the development of vaccines against otitis media. Intramural scientists are collaborating with scientists at the National Institute of Child Health and Human Development, NIH, and the Center for Biologics Evaluation and Research, FDA, to identify suitable antigen (foreign protein) candidates for conjugate vaccines.

Glutamate is the major excitatory neurotransmitter in the mammalian brain, and an extensive family of receptors mediate its actions. Evidence links glutamate receptors to a range of neuronal functions including synaptic development and plasticity, learning, and memory. Ironically, glutamate and glutamate agonists are neurotoxins and can result in neuronal degeneration and death. Glutamate receptors may be involved in disorders such as stroke, epilepsy and some neurodegenerative diseases. Glutamate receptors have been implicated in the degeneration of sensory cells and endings of the hearing nerve which follows acoustic overstimulation. The NIDCD intramural Laboratory of Neurochemistry is studying intensely the molecular properties of the glutamate receptor family.

The NIDCD is supporting studies on the regeneration of sensory c cells. The first breakthrough in adult mammals occurred with the regeneration of vestibular hair cells. Most recently, investigators have demonstrated hair cell regeneration in the culture of tissue removed from the human inner ear. Continued research in sensory cell regeneration could provide much needed progress in the amelioration of sensory hearing loss and tinnitus. This first breakthrough in human hair cell regeneration must be exploited quickly for the benefit of millions of hearing-impaired Americans.

Similarly, studies of smell and taste sensory cell regeneration may play a major role in research on the therapeutic repair of the central nervous system. Recent olfactory (smell) sensitivity research demonstrated in individuals with genetically determined specific anosmia (loss of sense of smell) the induction of olfactory sensitivity by repeated exposure to a specific odor. This finding would suggest a stimulus-induced plasticity in a sensory receptor neuron and a novel form of gene expression. This concept opens a new area of molecular biologic research and provides a basis for a new form of treatment.

Intramural scientists of the Voice and Speech Section have led in developing new treatments for patients with neurogenic voice disorders. They also introduced the first human use of botulinum toxin Type F for spasmodic dysphonia. Its injection on one side of the voice box results in muscle effects on both sides suggesting central nervous system changes. The physiologic bases for these changes are now being studied.

Application of modern technology to speech assessment is allowing investigators to examine trigeminolaryngeal reflexes in stuttering, physiological correlates of stuttering, developmental trends in childhood stuttering, and stuttered and disordered phonology in young children.

Studies of language and cognitive development in retarded children have previously indicated that language ability tends to be at or below other cognitive domains. Recent studies of children with Williams syndrome (WMS), conducted by NIDCD-supported scientists, have challenged the tenet that language is constrained and paced by cognitive skills. WMS, a rare genetic disorder, is characterized by mental retardation and distinctive facial features, cardiac and dental anomalies, and an excess of calcium in the blood causing fatigue, muscle weakness and depression. Additonally, WMS children have a most interesting and unique behavioral profile: linguistic abilities selectively developed in the face of severe general cognitive deficits. When compared with Down syndrome children, young children with WMS have a different cognitive phenotype, showing retardation in all developmental milestones, including language. Although young WMS children and children with Down syndrome are remarkably similar in their profound and equivalent delays, they follow different trajectories of development to adolescence, at which point they exhibit dramatically different language skills. WMS adolescents have relatively well developed semantic abilities. This research is examining differences between the two groups and analyzing language development in order to explain the contrasts between the two groups exhibited in adolescence. These studies are expanding our understanding of brain and behavior relations.

The NIDCD has begun the Partnership Program, a comprehensive minority research and training demonstration program with academic centers which have large enrollments of minority persons under-represented in biomedical and behavioral research. Students who are deaf or hard of hearing are also underrepresented in biomedical and behavioral research. Through a Memorandum of Understanding between the Office of Research on Minority Health and the NIDCD, this Partnership Program will provide support for improvement of curriculum and current research activities in the academic centers, and for the exchange of students, scientists, and administrators in order to maximize the opportunities for underrepresented persons to participate in fundamental and clinical research in human communication. These academic centers are: The Morehouse School of Medicine/Atlanta University Complex; University of Alaska System; University of Puerto Rico; and Gallaudet University.

Now that the NIDCD is five years old, there is a steady flow of impressive and significant research in each of the seven program areas. NIDCD support has stimulated training. Both extramural and intramural research opportunities have been created, and those training opportunities are in basic laboratories and in clinical settings. The National Multipurpose Research and Training Centers are thriving examples of what happens when one integrates outstanding scientists into a team, extends training opportunities and provides regional resources for the public. The NIDCD fifth anniversary was a moving celebration of science. Investigators presented the newest, the best science and, importantly, gave force and direction for the future. The NIDCD is fulfilling a promise to improve life for 46 million Americans who are challenged by disorders of hearing, balance, smell, taste, voice, speech or language.

Mr. Chairman, the 1995 budget request is $167,129,000.

Mr. Chairman, I would be pleased to try to answer any questions you have.

JAMES B. SNOW, JR., M.D.
Director
National Institute on Deafness and Other Communication Disorders
National Institutes of Health

Born: March 12, 1932, Oklahoma City, Oklahoma

Marital Status: Married, three children

Education: B.S., University of Oklahoma, Norman, Oklahoma, 1949-52; M.D., Harvard Medical School, Boston, Massachusetts, 1952-56

Professional History: Intern in Surgery, Johns Hopkins Hospital, Baltimore, MD, 1956-57; Resident in Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, MA, 1957-60; Captain, Consultant in Otolaryngology; U.S. Army Medical Corps, 8th U.S. Army, 121st Evacuation Hospital, Korea, 1960-61; Otolaryngologist, U.S. Army Hospital, Fort Leonard Wood, MO, 1961-62; Assistant Professor and Vice-Chairman, Department of Otorhinolaryngology, University of Oklahoma Medical Center, Oklahoma City, OK, 1962-64; Professor and Head, Department of Otorhinolaryngology, University of Oklahoma Medical Center, Oklahoma City, OK, 1964-72; Professor and Chairman, Department of Otorhinolaryngology and Human Communication, University of Pennsylvania, School of Medicine, Philadelphia, PA, 1972-90; Director, National Institute on Deafness and Other Communication Disorders, Bethesda, MD, 1990-.

Society Affiliations: Alpha Omega Alpha; American Academy of Facial, Plastic and Reconstructive Surgery; American Academy of Otolaryngology-Head and Neck Surgery; American Association for the Advancement of Science; American Broncho-Esophagological Association; American College of Surgeons; American Laryngological Association; American Laryngological, Rhinological and Otological Society; American Medical Association; American Neurotology Society; American Otological Society; American Society for Head and Neck Surgery; American Speech-Language-Hearing Association; Association for Chemoreception Sciences; Association for Research in Otolaryngology; Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum; International Bronchoesophagological Society; Massachusetts Eye and Ear Infirmary Alumni Association; New York Academy of Sciences; Pan American Association of Otolaryngology and Broncho-Esophagology; Phi Beta Kappa; Sigma Xi; Society for Ear, Nose and Throat Advances in Children; Society of University Otolaryngologists-Head and Neck Surgeons.

Honors and Awards: Regent's Award for Superior Teaching, University of Oklahoma, 1970; Certificate of Award, American Academy of Ophthalmology and Otolaryngology, 1971; Honorary Master of Arts, University of Pennsylvania, 1973; Second Vice-President, American Academy of Ophthalmology and Otolaryngology, 1973-74; Consulting Professor, Shanghai Second University of Medical Sciences, Shanghai, People's Republic of China, 1985; Honorary Fellow, Japan Broncho-Esophagological Society, 1985; Golden Award of the International Federation of Oto-Rhino-Laryngological Societies, 1989; Society of Scholars, Johns Hopkins University, 1991; Honorary Member, Association of Otolaryngologists of India, 1992; and Distinguished Achievement Award, Deafness Research Foundation, 1993.

Ms. PELOSI. Thank you very much, Dr. Snow.

Next we are going to hear from the National Institute of Aging from Dr. Hodes, please.

OPENING STATEMENT

Dr. HODES. Thank you Madam Chair. It is a privilege to appear before this Committee representing the National Institute on Aging.

The National Institute on Aging has the unique mission of conducting biomedical, behavioral, and social research related to the aging process, for the purpose of preventing disease and other problems of aged, and for maintaining the health and independence of older Americans. The responsibility of the National Institute on Aging has expanded as a direct result of the success of research funded by all of the Institutes at NIH which has had the common effect of extending life expectancy. These successes have converged to create a kind of demographic imperative as more Americans survive to increasingly older age.

To successfully serve its mission, NIA must maintain a balance between basic and applied research: findings that result from investment in basic research, both biological and behavioral, establish the basis for subsequent developments in detection, treatment, or prevention interventions. Often, important new clinical discoveries are the direct result of work in areas of basic research that were not initially known to be related to the diseases on which they now impact. For example, the ApoE4 work related to Alzheimer's disease which I will describe for you, would not have been possible without the knowledge gained from previous support by the Heart Institute for basic research on ApoE which normally functions as a carrier of blood lipids.

Another example of unanticipated discovery was last year's identification of the specific gene defect responsible for certain cases of another neurological disease, ALS, otherwise known as Lou Gehrig's disease. This breakthrough was the immediate consequence of the research of an NIA grantee, who was studying antioxidant enzymes related to aging and the nervous system.

ALZHEIMER'S DISEASE

To return to Alzheimer's disease as an example of the problems affecting older persons, it is an affliction which we are all too well aware of, currently affecting approximately 4 million Americans at an annual cost estimated at $100 billion. The past year has seen particular excitement about identification of what appears to be a major risk factor for Alzheimer's disease, namely a particular form of the ApoE gene. Now having identified ApoE as a risk factor in a substantial proportion of Alzheimer's patients, the NIA is committed to extend epidemiologic studies to understand how widespread this risk factor is among various groups, such as minority populations, and between genders. Ultimately, the real importance of identifying risk factors is that they provide opportunities to delve into the mechanisms of disease. NIA will be supporting research aimed at determining the role of ApoE and other defined gene products in the pathology of Alzheimer's disease, and at using this knowledge to devise strategies for treatment and prevention.

AGING RESEARCH

Research on aging offers an opportunity to reduce many of the risk factors that lead to the need for costly, long-term care and the loss of independence among older Americans. Recently, NIA has focused attention on treating degenerative conditions such as osteoporosis, which was mentioned earlier by Dr. Shulman, osteoarthritis, and muscle atrophy through replacement therapy with "trophic" factors such as hormones. These factors promote growth and maintenance of tissues such as bone, muscle, and cartilage. NIA will continue to emphasize support for these lines of research as well as basic studies to understand and modify age-related changes in bone metabolism and bone cell activity.

Many of the disorders and problems that older Americans face can be best attacked by addressing the behavioral and/or social, as well as the biological aspects of the problem. Information gained from NIA-supported research will provide the basis to develop strategies to maintain independence and productivity with advancing age, such as the increased use of assistive devices.

NIA research is proposing to develop cognitive and other non pharmaceutical interventions to maintain and promote independent functioning among older adults who are at-risk for decline in cognitive or perceptual abilities.

This work will enable the identification of the most effective methods to reduce both need for assistance and injuries.

SPECIAL POPULATIONS

Many important questions surround the health implications of menopause and hormonal changes in women. NIA will continue funding for newly initiated research on the natural history of menopause and the decline in ovarian function. This initiative will characterize the biological and psychosocial aspects of menopause and its effects on risk factors for age-related disease. In addition, NIA will continue support for its ongoing Women's Health and Aging Study which is designed to determine what diseases and other predisposing events cause and influence disability in women age 65 and older.

NIA also has a strong commitment to research which focuses on minority populations and the significant differences which exist between them and non-minority populations, such as their relative risk for specific diseases and disabilities, and their use of long-term care services. An example of this commitment is the NIA initiative developed to specifically recruit African-American and Hispanic populations for dementia studies through the establishment of 27 satellite centers as a part of the Alzheimer's Disease Research Centers program.

HEALTH OF OLDER POPULATION

All issues related to aging, including research sponsored by NIA, take on a heightened level of importance in the face of the demographic changes that will soon markedly raise the median age of

America's population. Ultimately, success in reducing morbidity, premature mortality, and the containment of national health care costs will depend upon research to develop the means to prevent, control, or cure those diseases and disorders that produce the greatest burden of human suffering and the need for costly long-term care.

The fiscal year 1995 budget request for the National Institute on Aging is $433,701,000. I will be happy to answer any questions.

[The prepared statement and biography of Dr. Richard Hodes follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute on Aging

Mr. Chairman, I am pleased to have this opportunity to present an overview of the research programs supported by the National Institute on Aging (NIA). In the short time that I have served as Director, progress in a number of critical research areas has given me and others in the field a heightened confidence that our research strategies will lead to the prevention or cure of the major diseases and disabilities in older Americans. Examples of these recent advances typify the diversity of NIA's portfolio: new insights into the association of the aberrant amyloid protein with Alzheimer's disease and the discovery of a genetic marker and potential risk factor for this disease; the successful preliminary testing of "trophic factors" to improve muscle strength in the elderly; new analyses revealing declines in the prevalence of 16 major chronic conditions in those above age 65; the use of transgenic technology to explore oxidative damage in animal models with the actual extension of life span; and the use of gene transfer techniques to combat the damaging effects of atherosclerosis in rodents, research that gives real promise for the development of a breakthrough treatment for cardiovascular disease.

As Director, I am challenged to maintain an essential balance between basic and applied research: findings that result from investment in basic research establish the basis for subsequent development in detection, treatment, or prevention interventions. Often, important new clinical interventions are the direct result of support for areas of basic research that were not linked at the time to the disease areas on which they now impact. For example, the "ApoE4" work related to Alzheimer's disease which I will describe for you, would not have been possible without the knowledge gained from previous support by NIH for basic research on ApoE which normally functions as a carrier of blood lipids. Another example of payoff in unforeseen areas was last year's discovery of the specific genetic defect responsible for certain cases of another neurological disease, ALS (otherwise known as Lou Gehrig's disease). This breakthrough was an unexpected and immediate payoff from the research of an NIA grantee, who was researching antioxidant enzymes as related to aging and the nervous system.

Returning to ApoE4 and Alzheimer's disease (AD), NIA-supported researchers recently found that expression of one form of the apolipoprotein E gene, ApoE4, is associated with an increased incidence of AD and could therefore be a major risk factor for AD. It will be necessary to confirm and better understand the association of ApoE4 with AD. Should ApoE4 indeed prove to be a major factor in determining AD susceptibility, modification of ApoE activity would become an attractive target for development of therapeutics. This and many other exciting discoveries are providing insights on how to solve the puzzle of this dread disease which now devastates over 4 million older

Americans and their families, with an annual cost of at least $90 billion.

NIA is supporting cutting edge research on the natural process of aging. One such initiative is focussed on the relationships between aging, oxidative damage, antioxidant enzymes, and antioxidant vitamins. Our cells must constantly resist the oxidative damage that occurs as a side effect of normal metabolism. We are keenly interested in discovering the exact mechanisms by which the body, through its own antioxidative enzymes, protects itself from this natural, but damaging, process. There is increasing evidence that certain nutrients, including vitamins C, E, and betacarotene, serve as agents to augment the body's natural protective mechanisms against cellular and subcellular oxidative damage. Preventive effects of antioxidants may have extraordinary potential to forestall a wide range of diseases such as cancer, ALS, AD, and cardiovascular disease. Additional research is necessary to build more evidence for these associations and to establish the safety for increased intake of these compounds.

Sixty percent of U.S. deaths are due to vascular disease, which has long stimulated NIA's interest in advancing research on age-associated vascular disease. During atherosclerosis (hardening of the arteries), some of the smooth muscle cells which are part of all normal arteries, begin to multiply and produce damaging proteins which are secreted into the walls of the artery. An NIA intramural research team has discovered that these arterial muscle cells, when placed in an environment that simulates arterial injury, proliferate within the artery and invade their surrounding membranes and proteins. The NIA research team is pursuing this line of research with the ultimate goal of developing therapeutic measures to reduce the extent of atherosclerosis, leading to a significant reduction in vascular disease and in health care costs.

Research on aging offers a real opportunity to reduce those many risk factors that lead to the need for costly long term care and the loss of independence among older Americans. One example is osteoporosis -- it affects over 25 million Americans, mostly women, and is a serious public health problem since associated fractures are a major cause of disability in older people. Costs associated with hip fractures alone exceed an estimated $7 billion annually. Recently, NIA has focussed attention on treating degenerative conditions such as osteoporosis, osteoarthritis, and muscle atrophy through replacement therapy with "trophic" factors. These factors promote growth and maintenance of tissues such as bone, muscle, and cartilage. In FY 1995, NIA will continue support for these lines of research as well as basic studies to understand and modify age-related changes in bone metabolism and bone cell activity.

Many of the disorders and problems that older Americans face can be best attacked by addressing the behavioral and/or social aspects of the problem. For example, one of our grantees has produced the first nationally-representative database on self-care behaviors practiced by community dwelling older Americans. Many more subjects reported compensating for their particular limitation by making modifications in daily routines, rather than by acquiring and using special equipment or devices or by making changes in their living environment. This and information gained from other NIA-supported research will provide the basis to develop strategies needed to promote the increased use of assistive devices and environmental change to maintain independence and productivity with advancing age. NIA is also pursuing research to develop cognitive and other non-pharmaceutical interventions to maintain and promote independent functioning among older adults who are at-risk for decline in cognitive or perceptual abilities. This work will enable the identification of the most likely methods to reduce both need-for-assistance and injuries.

Many important questions surround the health implications of menopause and hormonal changes in women. NIA will continue support for its ongoing Women's Health and Aging Study which is designed to determine what diseases and other predisposing events cause and influence disability in women age 65 years and older. NIA will also continue funding for newly initiated research on the natural history of menopause and the decline in ovarian function. This initiative will characterize the biological and psychosocial aspects of menopause and its effects on risk factors for age-related disease.

NIA also has a strong commitment to research which focuses on minority populations and the significant differences which exist between them and non-minority populations, such as their relative use of long term care services. Another example of this commitment is the particular initiative NIA developed to specifically recruit African-American and Hispanic populations for dementia studies through its Alzheimer's Disease Research Centers program.

All issues related to aging, including research sponsored by NIA, take on a heightened level of importance in the face of the "graying of America": those demographic changes that will soon markedly raise the median age of America's population as the baby-boom generation ages. Ultimately, success in reducing morbidity, premature mortality, and the containment of national health care costs will depend upon research to develop the means to prevent, control, or cure those diseases and disorders that produce the greatest need for costly long term care.

Mr. Chairman, the FY 1995 budget request for the National Institute on Aging is $433,701,000. I will be happy to answer any questions.

BIOGRAPHICAL SKETCH
Richard J. Hodes, M.D.
Director, National Institute on Aging

DATE AND PLACE OF BIRTH: December 31, 1943; New York, New York

CITIZENSHIP: United States

MARITAL STATUS: Married, one child

EDUCATION:

1965 - B.A., Yale University (summa cum laude), New Haven, Connecticut
1971 - M.D., Harvard Medical School (magna cum laude), Boston, Massachusetts

BRIEF CHRONOLOGY OF EMPLOYMENT:

1968 - 1970 -	Research Fellow, Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden
1971 - 1973 -	Intern and Resident, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
1973 - 1975 -	Clinical Associate, Immunology Branch, National Cancer Institute (NCI), NIH
1975 - 1976 -	Investigator, Immunology Branch, NCI, NIH
1976 - 1988 -	Senior Investigator and Chief, Immunotherapy Section, Immunology Branch, NCI, NIH
1978 - 1979 -	Clinical Fellow, Medical Oncology, NCI, NIH
1980 - 1981 -	Acting Chief, Immunology Branch, NCI, NIH
1983 - 1988 -	Deputy Chief, Immunology Branch, NCI, NIH
1984 - 1985 -	Acting Chief, Immunology Branch, NCI, NIH
1988 - 1993 -	Senior Investigator, Experimental Immunology Branch, NCI, NIH
1991 - 1993 -	Chief, Immune Regulation Section, Experimental Immunology Branch, NCI, NIH
1993 - -	Director, National Institute on Aging, NIH

SOCIETIES:

Diplomate, American Board of Internal Medicine; Board Eligible - Medical Oncology; American Association of Immunologists, 1974 to present; Associate Editor, Journal of Immunology, 1977-1979; Program Coordinator, U.S.-Japan Cooperative Cancer Research Program, 1982 to present; Section Editor, Journal of Immunology, 1985-1989; Chair, Program Committee, American Association of Immunologists, 1986-1988; American Society for Clinical Investigation, 1987 to present; Advisory Editor, The Journal of Experimental Medicine, 1990 to present; Associate Editor, Therapeutic Immunology, 1992 to present; Scientific Advisory Council, Cancer Research Institute, 1992 to present.

HONORS AND OTHER SPECIAL SCIENTIFIC RECOGNITION:

Phi Beta Kappa
Alpha Omega Alpha
Commendation Medal, PHS, 1977
Outstanding Service Medal, PHS, 1988

Ms. PELOSI. Thank you very much.

I thank all of you and thank you, Dr. Varmus, for being with us here today. Feel free to respond to any questions I may be putting to the witnesses.

There is a great deal of interest on our Committee in all of the issues that were discussed here today, but as you are aware, because of the death of President Nixon and the National Day of Mourning that the President has called for tomorrow, there is some question about whether there will be any votes until late Thursday, and some Members are not here in town and some are going directly to the funeral tomorrow in California.

But they have given me some questions and I know that they have or will review your very important testimony that will serve us well as we mark up the bill.

I wanted to start with Dr. Shulman.

Thank you again for your testimony Dr. Shulman. Since Dr. Hodes toward the end of his testimony was talking about women, I will begin my question in that vein with you.

One of the osteoporosis groups has testified that the Women's Health Initiative funded in the Office of the Director will not provide new information about this disease and instead will only confirm prior findings with the use of a larger sample group.

What is your view of this comment?

Dr. SHULMAN. I am not sure I fully understand the question.

Would you please repeat the question? What did they say?

WOMEN'S HEALTH INITIATIVE

Ms. PELOSI. They said that the Women's Health Initiative funded in the Office of the Director will not provide new information about osteoporosis and instead will only confirm prior findings with the use of larger sample groups. It might be scientifically valid, but I think the point is that it is not breaking any new ground in terms of the research.

Dr. SHULMAN. I will give my personal view and then ask Dr. Varmus to comment.

I think the Women's Health Initiative is addressing important questions with studies involving sufficiently large numbers of women. This will make a powerful difference between the smaller studies that have been carried on in the past and those that are being carried out now.

Dr. VARMUS. As you know, the design of the Women's Health Initiative has received a number of criticisms and this issue in particular was addressed by the Institute of Medicine in its review of the Women's Health Initiative. The recommendation by that Committee was that this phase of the study was entirely justified and that useful, new information would emerge from treating a large number of women with vitamin D and calcium and comparing them with appropriate control groups.

Dr. SHULMAN. As a matter of fact, those questions have not been fully addressed. In fact, NIAMS is holding a consensus conference in June, as I indicated in my testimony, on what the optimal level of calcium intake is. At that time, new data will be presented and judged by a panel.

Dr. VARMUS. I would make another point about this matter. As Dr. Shulman has pointed out to you, there are now new indications of identifiable risk factors for osteoporosis—for example, receptors for vitamin D.

In the context of the large study being undertaken through the Women's Health Initiative, it will be possible to collect samples that allow us to assess women who are receiving various treatments with respect to these newly defined markers, because one of the purposes of the Women's Health Initiative is to identify a large group of women, some of whom are undergoing observations, and some of whom are being treated. Samples will be taken that will allow the appropriate assessment for newly defined risk factors. It could be very important in learning in the long run who is at special risk for osteoporosis.

Ms. PELOSI. I appreciate that. Thank you, Dr. Varmus.

The Women's Caucus will be testifying on Thursday, and will be coming in with the Legislative Women's Health Initiative. I will be pleased to have that information that you supply me with to tell them, as well as your information, Dr. Shulman.

SPECIALIZED CENTERS OF RESEARCH

Dr. Shulman, our Chairman wanted me to ask you a question about budget justifications. Your budget justification indicates that some of the applications for specialized research centers in the recent recompetition were weak and that as a result, you have allocated funds to centers in other subject areas. Has this caused you to reevaluate your use of the Specialized Centers of Research (SCOR) mechanism?

Dr. SHULMAN. The Specialized Centers of Research program started in 1987 with the awarding of three grants each for three major diseases: Rheumatoid arthritis, osteoarthritis, and osteoporosis. We had the major recompetition, as you say, in 1992.

The result of this competition was that we had seven highly meritorious applications. Four of those were in rheumatoid arthritis, one was in osteoarthritis, and two were in osteoporosis.

We had not had any experience with these centers prior to the original award, and in the ensuing years we found that a limiting factor on quality was whether or not there was a body of clinical investigations and a group of clinical investigators ready to use this particular mechanism.

This type of specialized center mandates the marriage between basic research and clinical research. At some of the original centers, there was enough basic research, but not enough clinical research to justify using the SCOR mechanism.

Now, at the same time, we had an initiative which was spawned and encouraged by this Committee, to do much more research on lupus. That was in 1993, if you remember. One of the ways by which we mounted our new Initiative on Lupus was to open a competition for specialized centers of research on systemic lupus, or SLE.

We received eight very good applications and we funded the two most highly meritorious ones. So what we are doing is using this mechanism in the very best way possible, by being flexible and making awards to the best applications.

Ms. PELOSI. I appreciate that. Thank you, Dr. Shulman.

You have mentioned finding a gene that predicts bone density and could be used as an early warning system for osteoporosis.

Should doctors begin genetic screening on the basis of this finding?

Dr. SHULMAN. Oh, no. We are not to that yet. This gene, as Dr. Varmus said, is actually for the receptor for vitamin D. What it does is to heighten the importance of vitamin D. This gene needs to be tested and evaluated in much larger and different types of populations than in the one population in which they have some data.

The data thus far is only on the basis of a sample of 341 people. We need to study much larger groups of patients.

Ms. PELOSI. Thank you for your answer.

NIMH INTRAMURAL PROGRAM EVALUATION

Dr. Cowdry, your budget justification mentions a stringent evaluation to redefine your intramural program. Intramural research comprises a larger share of your research portfolio than the NIH average. With the staffing reductions required of your Institute, are you considering downsizing your intramural program, and what issues is the evaluation expected to address?

Dr. COWDRY. Ms. Pelosi, there are a couple of comments to put this in perspective. First of all, our intramural program actually started out at approximately 30 percent of our Institute's budget. It is now reduced to approximately 15 percent in the current year.

So there has already been a progressive process over the last decade of downsizing by one-half of the intramural program. In part that is because the intramural program originally was, to a great extent, the place from which researchers were seeded across the country. That process has been very successful.

Clearly, as part of the overall NIH evaluation of what intramural research does best, we have our own evaluation to do, particularly since our program is still slightly larger percentage wise.

The evaluation will involve our outside board of scientific counselors looking carefully at the balance of basic and clinical research and at all the branches individually to assess the quality of their science and to make recommendations about resource allocation in the intramural program. We have already made a decision to condense inpatient units in the clinical center, and we are proceeding with the scientific evaluation of the program.

It fits, of course, in a way with the downsizing of the Federal Government in general. I think the major issue we face, which has been touched on in other testimony, really has more to do with the reduction of Grades 13, 14, and 15 and above employees in our scientific environment. That reduction will cause a problem in the intramural programs throughout the NIH and certainly our Institute.

Apart from that, I think that we expect to perform this evaluation.

Ms. PELOSI. Do I conclude from your comments that your review is likely to result in a change in the Institute's uses of the clinical center?

Dr. COWDRY. Yes, indeed that is already planned in terms of the space we occupy. We currently have 5.5 inpatient units and those will be condensed. At this point, that will result in a cost savings and improve the efficiency of the program, but a decision hasn't been made about any reduction in the number of patient days, for example, and how those would be allocated among our various programs. We believe we can do the same work more efficiently with this change.

MINORITY TRAINING PROGRAMS

Ms. PELOSI. Your Institute, Dr. Cowdry, has developed minority training programs that are different from the NIH wide programs. Is this an artifact of not being part of NIH in the past years or have you identified needs not being met by the standard NIH programs?

Dr. COWDRY. Well, I would say that in part it is a product of being out of the NIH network, in part of special needs. I think again the need for more biomedical research is large and it is across the field.

We have placed a particular emphasis in minority research on the development of researchers and more recently on the strengthening of infrastructure, both through the initiative that we share with the NIH generally and the more recent initiative to build the research infrastructure of departments of psychiatry at historically black colleges and universities. So to the extent that we have opportunities to strengthen, in this case, departments of psychiatry in minority institutions, we have taken particular initiative in doing so.

Ms. PELOSI. Thank you very much, Dr. Cowdry.

STRATEGIC RESEARCH PLAN

Dr. Snow, you have been on a schedule of updating two of the seven research areas in your strategic plan each year.

Are you still on this schedule? What research areas are you currently updating?

Dr. SNOW. In January of 1994, we updated the Language and Language Impairment Section and in March of 1994, we updated the Balance and Balance Disorders Section.

We have been on a three-year cycle in which there would be a complete updating of the National Strategic Research Plan by doing two of the six sections every year. When the National Strategic Research Plan was developed in 1989, the year after the Institute was created, somewhat different instructions were given to the consultants who developed the plan as opposed to the instructions that were given to each of the groups that did the updating for the last three years.

Now, for the first time we are repeating the cycle beginning with language and balance in January and March. And at the end of that process, both groups of experts said to us: It isn't necessary to do this every three years; there should be a longer interval between updates. And taking that advice, along with the need to reduce expenses in every way possible, we are now starting a longer cycle of six years, updating just one section per year, and that first section will be the Voice Section in January of 1995.

That means that there will be six years between updatings. We do have a Research Priority Subcommittee of our National Advisory

Board that will examine each area midway through the cycle, so that it won't be six years but actually more like three.

Ms. PELOSI. I appreciate that. Thank you.

PARTNERSHIP PROGRAM

I want to ask you about your Partnership Program and how it differs from the minority training and support programs already conducted at NIH.

Is the Office of Research on Minority Health funding the partnership program?

Dr. SNOW. Yes. They are funding all of the partnership that deals with minorities such as African-Americans, Hispanic-Americans and Native Americans or Alaskan natives. We also have a partnership with Gallaudet University in that we recognize the deaf community as a minority group. That part of the partnership is not funded by the Office of Minority Research.

ASIAN–AMERICANS

Ms. PELOSI. Did I miss something or did I not hear you say anything about Asian-Americans?

Dr. SNOW. We don't consider Asian-Americans as being underrepresented in biomedical or behavioral research. Actually, they are quite well represented and we do not have an Asian-American——

Ms. PELOSI. Do we know this empirically or anecdotally or scientifically? How do we know they are so well-represented?

Dr. SNOW. We have definite evidence in our portfolio of their strong representation.

Ms. PELOSI. Is that typical at NIH?

Dr. VARMUS. That is true across the board at NIH, yes.

Ms. PELOSI. Do they agree? Have you had any concerns expressed by the Asian-American community that they are sufficiently represented?

Dr. VARMUS. There may be subpopulations of Asians who might find themselves underrepresented in either patient categories or among the scientists, but to the extent that we have looked at this, they are overrepresented with proportion to the numbers that are present in the U.S. population.

Ms. PELOSI. With all the greatest respect, just where is that decision made? Is that something that is subject to evaluation from one year to the next? Is it a decision that was made?

Dr. VARMUS. This is not a decision. This is a number. For example, if one asked how many people who identify themselves as Asian-Americans are present in the grant review process at NIH or among scientists with tenure, as a proportion of the population, they are overrepresented.

Dr. SNOW. For example, minority supplements are not authorized for Asian-Americans. Now, for Pacific Islanders, yes, but other Asians are not covered. So we can make awards for minority supplements for African-Americans, Hispanic Americans, Native Americans, Alaskan Natives, and Pacific Islanders.

Ms. PELOSI. I see. So legislatively you are directed in the direction you just described?

Dr. SNOW. Yes.

Ms. PELOSI. The evidence demonstrates to you, Dr. Varmus, that the area is covered as far as what you see in terms of——

Dr. VARMUS. We have numbers on these. I don't have them with me today, but I will be happy to submit them for the record.

[The information follows:]

ASIAN AMERICANS IN BIOLOGICAL SCIENCE

The National Institutes of Health (NIH) bases its distribution of minority supplements on data compiled by the National Science Foundation (NSF) in a biennial report to Congress on the status of women and minorities in science and engineering professions. The publication, entitled Women and Minorities in Science and Engineering: An Update, last published in January 1992, indicates that Asian Americans are well represented in the fields of biology and medicine.

The following table compares numbers of specific minorities in biological and medical scientific professions employed in 1989 with the percent of each minority in the total population and total workforce. It is evident from this data that Asian Americans are not underrepresented in these professions. With respect to the total population, Asian Americans represent 2.0 percent of the total workforce and 3.0 percent of the total population. With respect to the total number of persons employed in the biological and medical professions in 1989 they represent 8.4 percent, approximately three times the number of Asian Americans in the total population, and approximately four times the number of Asian Americans in the total workforce.

COMPARISON OF RACIAL/ETHNIC GROUPS EMPLOYED AS BIOLOGICAL AND MEDICAL SCIENTISTS 1/

Data compiled from 1989 by the National Science Foundation
Published January, 1992

Profession/Employed Race	Black	Asian	Native American	Hispanic	Total Employed by Profession
Biological Scientists	851	5,670	61	1,128	67,250
Medical Scientists	636	2,656	89	495	32,079
Total Biol./Medical Scientists	1,487	8,326	150	1,623	99,329

PERCENT OF RACIAL/ETHNIC GROUPS TO TOTAL BY PROFESSION 1/

Data compiled from 1989 by the National Science Foundation
Published January, 1992

Profession/Employed Race	Black	Asian	Native American	Hispanic	Total by Profession
Biological Scientists	0.9%	5.7%	0.1%	1.1%	67.7%
Medical Scientists	0.6%	2.7%	0.1%	0.5%	32.3%
% of Total Bio/Med Scientists	1.5%	8.4%	0.2%	1.6%	100.0%
% of Total Workforce	11.0%	2.0%	2/ n/a	5.0%	▨
% of Total Population	12.0%	3.0%	2/ n/a	8.0%	▨

1/ Data taken from Table 3 (pg. 81) of "Women and Minorities in Science and Engineering: An Update".

2/ The lack of reliable data on Native American scientists makes it difficult to accurately their participation in this profession with their representation in the general workforce.

Ms. PELOSI. I would appreciate that very much, thank you. Because in the district that I represent I am always proud to say how proud we are of Dr. Varmus.

And whether it is Chinese medicine or other therapies or whatever else, the Asian-American community brings very specific concerns to us when we talk about, for example, health care reform and I know that those involved in clinical trials and those who are professionally involved in those trials have special needs.

Dr. VARMUS. As you know, our new inclusion guidelines for clinical studies require attention not only to large minority populations like Asians, but subgroups within those populations.

Ms. PELOSI. Thank you, Dr. Varmus.

RUBELLA AND DEAFNESS

Dr. Snow, may I ask you, when you are looking at all the different ways to improve the situation as far as deafness and other communication disorders and you are looking genetically, et cetera, where does something like rubella come into play for you since it is not genetic?

Dr. SNOW. Right. That is an infectious disease. Maternal rubella, which fortunately has been largely eliminated in the United States by the immunization of young girls. Unfortunately, it is still——

Ms. PELOSI. As far as the future is concerned.

Dr. SNOW [continuing]. A major problem in other parts of the world. For example, in India, there is no immunization against rubella and so the epidemics of maternal rubella continue in India, producing not only deafness and blindness but also heart defects.

Ms. PELOSI. You don't see any intervention at the research level to correct that?

Dr. SNOW. Well, we have a very good solution for that problem—to just carry out the cost-effective immunization—but in a country like India where there are so many competing demands for the health dollar, the Ministry of Health has made the decision not to vaccinate against rubella, as strange as it seems to us, and it remains a very major problem.

I am sorry. I got off your question.

Ms. PELOSI. I understand what you are saying. You have answered me very well.

I understand that the future looks fine for the U.S.; unfortunately, not so for India. But I just meant for those, say, women of my age whose children might have been affected by such a sad occurrence on the part of maternal rubella that there is nothing in research that can intervene there.

Dr. SNOW. We have excellent prevention in the infectious diseases that produce deafness. Mumps and measles can be prevented by immunization. Now we have the very effective Hemophilus Influenza Type B vaccine against meningitis that used to produce one-fourth of the cases of acquired deafness in children.

What remains as the major problem is hereditary hearing impairment, and virtually all hearing impairment is either hereditary or it has a genetic basis in the predisposition. Even in conditions like noise-induced hearing loss, where there is obviously an environmental factor, the noise, there is still a hereditary predisposition for noise-induced hearing loss. Different individuals have different susceptibility to it, so therefore it is important for our Institute as well as other Institutes to make major investments in molecular biology, specifically molecular genetics because that is where the rapid progress can be made in this decade.

HEARING AID RESEARCH

Ms. PELOSI. I certainly hope so. As far as those who are already afflicted, we understand that you plan to conduct a hearing aid trial in fiscal year 1995?

Dr. SNOW. Yes.

Ms. PELOSI. Will the trial be testing new technologies or refining the appropriate use of existing devices?

Dr. SNOW. In it, we will be trying to determine the proper role of existing devices. There have been no scientific clinical trials of hearing aids. All of the clinical trials of hearing aids have taken place in the marketplace. If a hearing aid doesn't sell well, it tends to disappear from the market.

It is our belief that there are subgroups of the hearing-impaired population that benefit from certain hearing aid strategies that already exist and we are going back to a very fundamental question: Is linear amplification better for certain individuals in the hearing impaired population as compared to dynamic compression amplification?

This is the most important question of all and it is the first to be addressed in the clinical trials.

Once we have the answer to that, then other questions for clinical trials will fall into place as part of this program with the Department of Veterans Affairs in the development of new devices. When those come on line, they will also be tested in the clinical trials. But we are starting out with existing, commercially available devices.

Ms. PELOSI. This sounds very interesting.

How much financial support is the Department of Veterans Affairs providing for your joint hearing aid project?

Dr. SNOW. For this clinical trial, $400,000.

Ms. PELOSI. Of a total cost of?

Dr. SNOW. One and a half million dollars. The NIDCD will be putting in 1.1 million.

Ms. PELOSI. Thank you very much, Dr. Snow.

NIA INTERNAL REVIEW

Dr. Hodes, we understand that you have conducted an office-by-office review of your Institute since coming on board as the new Director.

What changes are in the works as a result of this review?

Dr. HODES. The approach I have been taking has been to take advantage of the skills and expertise in our Institute by providing a more extensive forum for interaction of our staff scientists. For example, we have made every effort to combine the skill of our intramural scientists and the perspective of extramural scientists through collective planning efforts. We have taken a scientific approach to determine areas of maximal need, and to identify scientific opportunities. We are working collectively and it has been a delightful experience.

So far it has not required restructuring or reorganization of offices, but rather a redefinition of the interactions and standards and processes for decision-making. We completed last winter the first of our scientific planning retreats at which senior Institute staff examined a collection of our most important priorities and discussed them in terms of scientific opportunities. Developmental tasks were assigned to groups of staff to provide specific recommendations regarding initiatives that will be discussed at a summer retreat. This is a planning process that should be most efficient in terms of identifying prime scientific opportunities.

ALZHEIMER'S DISEASE

Ms. PELOSI. There seems to have been a shift in emphasis during the last year in Alzheimer's research from amyloid proteins to genetics.

Do you expect a comparable shift in the Alzheimer's research portfolio or do you even accept the first premise?

Dr. HODES. Amyloid research and genetics research are by no means mutually exclusive. In fact, they are faces of the same integrated process. Amyloid is a material abnormally accumulating in the brain of patients with Alzheimer's disease, and is a product whose accumulation is influenced strongly by genes. Some of the early epidemiology and familial descriptions of Alzheimer's disease—in small numbers of patients in specific families—describe a number of mutant types in the amyloid gene itself.

Despite their relatively small numbers, this provided a critical first approach to understanding the biochemistry as well as genetics of the disease. The change in emphasis has really come about by the supplementation of this existing information about amyloid with the discovery of ApoE as a risk factor in Alzheimer's disease.

It is important because rather than a risk factor for small numbers of individuals with particular families, this appears to have the potential for identifying a risk factor that will be in common to a larger number of individuals. I should stress that the epidemiology of ApoE is very much in process and we await anxiously a number of ongoing studies to better define it.

The genetics studies are the forerunner of other studies which will allow us to identify mechanisms and hopefully, eventually the means of intervening. In the case of the ApoE gene, its identification as a risk factor has now led to interest in analyzing the role of the molecule it encodes and how it forms itself in the disease.

There are a number of very interesting laboratory findings which indicate that the different forms of ApoE associate differently in the test tube with the beta amyloid. Rather than there being a tension or competition between amyloid and ApoE or other gene products in Alzheimer's research, the greatest promise lies now in a richer understanding of multiple genes, multiple products, and their potential interactions.

And the hope is that this greater understanding is going to translate into the identification of the biochemistry and the genetics of the Alzheimer's lesion, pointing a way towards correcting those lesions by appropriate interventions.

Ms. PELOSI. I can conclude from your answer that this genetic approach related to the ApoE has been generally accepted by the research community?

Dr. HODES. I think this was a remarkable demonstration of the effectiveness of the infrastructure in this research area. From the time that the first report appeared of apparent epidemiologic association between ApoE4 and the risk of Alzheimer's until the time it was confirmed in a number of laboratories was measured in months. It was the good fortune of having a number of established research studies with an established population on whom researchers can then go back and reexamine patients for ApoE and confirm the epidemiology.

I think there is no question that multiple studies have confirmed that ApoE can represent a risk fa¢tor. Once again, how extensive and how this will sort by different populations, gender and ethnic differences will be revealed by ongoing studies, but is not just completely clear.

Ms. PELOSI. Just in closing, in past years your Institute has testified that its research goal for Alzheimer's was to delay onset of the disease by five years.

Is this still your guiding principle or have research breakthroughs changed that?

Dr. HODES. I have to say that my own temperament resists strongly the naming of goals of this sort. I understand their utility if they provide targets, but I think that is far outweighed by raising false hopes.

Ms. PELOSI. Thank you very much, Dr. Hodes.

Mr. Porter.

Mr. PORTER. Thank you, Madam Chair.

NIH COST SAVINGS BOOK

Gentlemen, I have been trying to make the point all of last week that biomedical research, contrary perhaps to popular perception, contributes greatly to reducing health care costs in terms of delivery of services. The NIA, the NIAMS and NIDCD all have entries in the NIH "Cost Savings Book." While I don't see one for the NIMH, you might certainly discuss lithium, a $6 billion annual savings, I understand. I wonder if each of you would comment briefly on the potential savings, the actual savings from biomedical research in terms of health care costs.

Dr. Shulman.

NIAMS COST SAVINGS

Dr. SHULMAN. I would be glad to start, Mr. Porter. The two different cost-savings areas that we have in the book are interesting. The first concerns lupus nephritis. Our intramural program has produced a 17-year study showing the beneficial effects of adding intravenous cyclophosphamide to prednisone therapy. This combination delays the appearance of kidney damage in lupus. What this does is prolong the time before the patient has to begin kidney dialysis or kidney transplantation, resulting in tremendous cost savings.

We invested about 12 million dollars in this research over 17 years, but the payoff has been a savings of about $117 million for each year thereafter as a result of this research.

The second cost-savings example relates to a therapy for psoriasis. We have discovered that psoralen, a light sensitizing drug, given in combination with ultraviolet A radiation can actually reduce the need for hospitalization of psoriasis patients. For severe psoriasis, patients used to have to come into the hospital often for treatment with tars and other substances. This discovery provides an annual savings of $77.5 million in reduced treatment costs and lost earnings.

I must say that I am very sensitive to the cost-savings issue, but I would also hope that emphasis be placed on quality of life measurements, as advances in total joint replacements, which have produced remarkable alleviation of pain and allowed people to keep mobile much longer. I don't know how they turn out from a cost savings standpoint, but I know there are remarkable benefits to mankind from the quality of life standpoint.

Thank you.

Mr. PORTER. Anyone else?

Dr. Hodes, would you like to comment?

NIA COST SAVINGS

Dr. HODES. Certainly, thank you.

The entry in the book to which you refer reflecting NIA support was the study of isolated systolic hypertension in the elderly. Up until the time of this study, it was widely presumed that diastolic hypertension was the real risk factor in disease and systolic hypertension was largely ignored. What this study demonstrated was that isolated systolic hypertension common in the older population was in fact a risk factor for cardiovascular and cerebrovascular disease. It showed that relatively inexpensive, safe, treatment with antihypertensives was able to reduce morbidity in terms of cardiovascular and cerebrovascular events. This was then an instance in which the technology already existed. But what was needed was a study to demonstrate efficacy.

Another example of a similar circumstance relates to the role of pneumonia as a common cause of morbidity and death in older Americans. Pneumonia, particularly that caused by pneumococcal bacteria is relatively straightforward to treat in younger populations, but is a more serious cause of morbidity and death in older populations. Moreover, there are clinically demonstrated effective vaccines now available for immunization against pneumococcal infections.

The NIA in cooperation with a number of government and outside agencies, is currently involved in a campaign to educate and disseminate information among health care professionals. It is planned that once physicians understand what to do when patients come to them with questions about immunization, the lay public will be educated. Indeed, immunization is now covered by most public compensations and it is eminently available as a mechanism for prevention of disease.

Mr. PORTER. Thank you.

Dr. Snow.

NIDCD COST SAVINGS

Dr. SNOW. I think two of the best examples of cost saving in our area are the early identification of hearing impairment in infants and young children and noise-induced hearing loss in industrial workers. To identify an infant early with hearing impairment is of tremendous importance.

Unfortunately, the average age of identification of hearing impairment in the United States is close to three years. It ought to be in the first several months of life so that special education can be started early and so that amplification can be utilized if there is any residual hearing.

It is difficult to quantify how much would be saved by doing this, by starting early and not having to catch up with the educational process beginning at age three. And although it is hard to come up with the specific figures, the savings would be enormous.

Likewise, in noise-induced hearing loss, we know how to prevent this form of hearing impairment, the prevention of it is based on research and the savings are enormous when it is applied.

The NIDCD took advantage of the opportunity within the legislation that created the Institute to form a Deafness and Other Communication Disorders Interagency Coordinating Committee. All of the Federal agencies which have some role in deafness and other communication disorders meet four times a year, and we gather the expenditures in deafness and other communication disorders.

In the hearing area, the annual expenditures by the Federal Government are $913 million. $103 million of that is for research and $810 million of it is for nonresearch expenditures, of which the Social Security Administration spends an estimated $268 million for Social Security Disability Insurance benefits for individuals on the basis of hearing impairment, and there are 45,800 such recipients. And they expend $312 million for Supplemental Security Income benefits to 53 thousand recipients. This is the magnitude of what can be saved through research.

Mr. PORTER. Thank you.

Dr. Cowdry.

NIMH COST SAVINGS

Dr. COWDRY. Mr. Porter, I assure you that our not being on the "savings list" is purely an artifact of our late arrival back at the NIH. If we were to put the sources of cost savings together, they would stretch really from efforts in simply treating mental disorders which results in savings documented in current reports to Congress to ongoing studies of preventive intervention approaches to behavior disorders in children.

I touched specifically on the issue of lithium and its savings over the last 20 years to society. $40 billion, in that range, analogous to what you noted as an annual cost saving. Treatment of depression results in decreases in morbidity, increases in productivity and decreases in the tragedy of suicide. The savings are substantial.

You can look specifically at studies that our services research effort had funded demonstrating that clozapine is remarkably cost-effective, even though it is expensive, because it reduces rehospitalization and thus produces very direct savings. The same savings can be shown for specific intervention programs which reduce rehospitalization. Many of the costs of mental illness lie in terms of looking at health care reform.

Indeed, our report on Health Care Reform for Individuals with Severe Mental Illness, which was provided to Congress, documents exactly this kind of savings and also documents other medical illness cost offsets whereby by treating mental illnesses such as depression you can actually reduce the expenditures in health care generally.

We can also look to longer-term effects of prevention, although they are harder to quantify at this point. That is one of the reasons why we are doing research in the AIDS area. The savings produced by efforts to reduce high-risk behavior will be somewhat difficult to quantify, but the costs savings with the prevention of a single case of AIDS are dramatic.

Similarly, in terms of behavior problems in childhood, if preventive interventions in schools, such as our family and schools together program, can be proven to be cost-effective at reducing later problem behaviors, we would demonstrate remarkable savings to society. That is more speculative but at least we are laying the research ground work for that kind of demonstration of cost savings.

Thank you.

Mr. PORTER. Thank you all very much.

Thank you, Madam Chair.

Ms. PELOSI. Thank you very much, Mr. Porter.

The Chair recognizes Mrs. Lowey.

Mrs. LOWEY. Thank you, Madam Chairwoman. And thank you all for appearing before us today.

I apologize for being detained but I appreciate your testimony and I look forward to further conversations with you.

EATING DISORDERS

I have a few questions which I would like to present for your comments. First of all, Dr. Cowdry, eating disorders are a major problem in many of our communities, particularly among adolescent women. I appreciated your comments concerning the cost-effectiveness of treating a whole range of mental illness and in my judgment, frankly, mental health problems should be treated equally with any kind of physical ailment. I am a great admirer of Tipper Gore's leadership on this issue.

Can you update the Committee on NIMH's collaboration with the American Psychiatric Association to develop treatments and guidelines for eating disorders?

Dr. COWDRY. Well, what I can tell you is that an effort is underway to develop those guidelines. We can report to you relative success at treating particularly bulimia as an eating disorder but anorexia nervosa has proven to be more resistant to treatment, as you know. And, indeed, one of the focuses of our research is to develop an effective treatment for both spectrums of eating disorders. I don't know the exact status of where those guidelines are currently, having been on the job for three hours now, but will be happy to provide that for the record.

There are, I think, other developments and possible collaborations emerging. For example the McKnight Foundation has just funded a $4.6 million program on research in eating disorders, including the use of a prevention module and development of educational tools. And I think there are opportunities for collaboration between our own public education efforts in eating disorders and the program that is planned by that foundation.

So I think there is much to be done, particularly in understanding the etiology that has made these disorders, particularly anorexia nervosa, somewhat difficult to treat.

[The information follows:]

In February 1993 the American Psychiatric Association issued Practice Guidelines for Eating Disorders. The NIMH provided expert commentary and an NIMH staff member (Harry E. Gwirtsman, M.D.) served as a reviewer.

Mrs. LOWEY. Has there been any implementation within our school public health programs as a result of the work? You talked about success with bulimia, and I wonder whether there are successful programs around the country on the community level, either in neighborhood health centers or in school health programs, that could be good examples of how to implement these findings?

Dr. COWDRY. We have had a research conference—and I am glad to see there is bipartisan interest in this issue as well; I know Mr. Porter has a long-standing interest in eating disorders—to look at what we know about etiology and treatment and to evaluate the readiness for a more broad-scale educational campaign aimed at both professionals and the lay audience.

One of the primary conclusions of the conference was that major efforts may be timely in helping primary care practitioners in particular, to identify these disorders at an early stage. Professional education might be a key component of this. The participants were not sure whether general education campaigns would be effective. In part this doubt is due to our lack of knowledge about the etiology of these disorders. Whether simply educating people about healthy eating habits actually lessens the prevalence of these disorders is not at all clear, because we don't fully understand the causes of these diseases.

We will certainly review possible education efforts. I think part of that review would also involve the Substance Abuse and Mental Health Services Administration in terms of their involvement in education related to the treatment of mental disorders.

Mrs. LOWEY. Thank you.

I would be interested to know whether successful models can be developed by a school system, obviously in terms of prevention, so I would look forward to continuing to work with you on this.

Dr. COWDRY. Certainly.

[The information follows:]

To the best of our knowledge there are no Federally-funded clinics specializing in eating disorders. In the May 1993 NIMH-sponsored conference on eating disorders, the participants evaluated the scientific readiness to develop an education campaign on eating disorders for the public and health-care professionals. The consensus of the conference was that although considerable effort is being expended on eating disorders research, the scientific knowledge base necessary to develop a successful campaign was not yet available. Also to our knowledge, there are currently no school-based eating disorders prevention programs. NIMH looks forward to the results of further research to guide the development of treatment, education, and prevention efforts.

BEHAVIORAL SCIENCE INITIATIVES

Mrs. LOWEY. I would also be interested in an update on the committee's efforts to develop a behavioral science research agenda, and that is tied into my previous question also.

Dr. COWDRY. Absolutely.

[The information follows:]

NIMH is continuing to focus on expanding its program of behavioral science initiatives. Much of the research in behavior medicine is based on the results obtained by more basic behavioral investigations. Some recently instituted activities include the Behavioral Science Task Force, the NIMHC enters for Behavioral Science Research, and the Behavioral Science Track Award for Rapid Transition (B/START) program. In addition, in April of 1994 a Program Announcement was issued on "Basic Research in Emotion," co-sponsored with NICHD and NIA. Examples of progress:

The NIMH Behavorial Science Task Force, Co-Chaired by Gordon Bower, Ph.D., and John Kihlstrom, Ph.D., was formed to assess progress and define opportunities for research in basic behavioral and social science related to mental health. The Task Force includes four members of the National Advisory Mental Health Council and 50 scientists serving as chairs and members of topical workgroups. A Report on the Task Force recommendations will be submitted by the Council to Congress within the next several months.

In FY 1993 the NIMH Centers for Behavorial Science Research were initiated. These Centers provide unified, integrated research environments in which to pursue novel and focused questions in basic behavioral science related to mental health. The centers are required to conceptualize and organize their work according to a broad multidisciplinary framework. Applications for FY 1994 funding currently are being solicited. Ongoing centers (initiated in FY 1993) are:

"Affective Style: Social and Biological Substrates," directed by Richard Davidson, Ph.D., at the University of Wisconsin, Madison. Individual differences in emotion-related processes are examined from several perspectives: (a) By measurement of neural, autonomic, and hormonal correlates; (b) by objective assessment and coding of affective behavior and interactions; and (c) by including, in addition to adult subjects, study of mother-infant interactions and monozygotic and dizygotic twins.

"Center for Developmental Science Research," directed by Robert Cairns, Ph.D., at the University of North Carolina, Chapel Hill. This center investigates the varieties of ways that the environmental context affects the course of development, and the ways in which this context interacts with biological predispositions. A core aspect is longitudinal developmental research on social and cognitive processes in community context; this detailed focus on human development is complemented by a investigation of animal models of aggression.

In FY 1994, NIMH also initiated the "Behavorial Science Track Award for Rapid Transition (B/START) Award," which provides quick turnaround support for small pilot projects in order to facilitate the entry of new investigators into the field of behaviorial science research. Applications for FY 1994 funding are currently being reviewed.

Mrs. LOWEY. There is a whole range of areas where this is important.

Dr. COWDRY. There are indeed. And in my previous testimony, I touched on some of the areas of preventive intervention that we are very actively involved in already. I think that in addition to the applied aspect of the behavioral sciences, the basic behavioral science we support is important because it provides the basis for designing cognitive behavior therapy or prevention interventions.

The status currently is that the task force report, which goes to Council in May, is in draft form. It will be debated by our Council in May and specific implementation plans will be developed. We look forward to reporting progress on this to you.

SERVICES RESEARCH AND EPIDEMIOLOGY STUDY

Mrs. LOWEY. Thank you.

When do you expect the NIMH to complete its multi-State child and adolescent study? Is that connected or separate from what you are saying?

Dr. COWDRY. You may be referring to the Services Research and Epidemiology Study that is just getting underway looking at services for children and adolescents in terms of mental illnesses.

Mrs. LOWEY. I was asked about this. Was that the study? I believe that was it.

Dr. COWDRY. That is just getting underway. We think it is absolutely critical. We know there is a substantial prevalence of mental illness in childhood and adolescence, but we do not have sufficient information about the details of this from an epidemiologic perspective, so that is one component of this study.

A larger component is health services research to look at how health services are organized to provide care to children and adolescents currently, and what the gaps are in current services. We know that there are substantial gaps. Substantial numbers of children and adolescents with disorders don't begin to get treatment. We expect that this study will produce the kind of data that is necessary to help guide health care planning. It has just started.

Mrs. LOWEY. When do you expect that study to be completed?

Dr. COWDRY. It is a several-year study and also includes a longitudinal component, so it will not be in the next year. It is a several year study.

Mrs. LOWEY. So it will be several years before we can even consider translating the results of the study into action, I imagine, or is there a plan? Is there an action plan associated with the study?

Dr. COWDRY. I am not fully familiar with that, so may I provide that for the record?

Mrs. LOWEY. Certainly. I appreciate that.

[The information follows:]

The NIMH multi-site study of child and adolescent service use, need, outcomes and costs will begin in September 1994. It is expected to be a five year project.

While results of this multi-site study will probably not be available for several years, there are other studies of child and adolescent service use that are near completion, which NIMH believes will be able to begin to illuminate servie use and needs for children and adolescents. These include a study at Fort Bragg of a comprehensive service system for children, adolescents, and their families. This study is headed by Dr. Leonard Bickman of Vanderbilt University. Results from this study will be available this year. A study of service integration for children (The California AB377), headed by Dr. Clifford Attkisson of the University of California, San Francisco, has already provided information about the effects of service integration on reducing the costs of residential care. Another study of children's services, conducted by Dr. Charles Glisson of the University of Tennessee, is examining the effects of coordinated systems of care for children in custody of the state of Tennessee. Results from this study indicate significant reductions in the use of restrictive placements for children receiving coordinated services.

An action plan for the NIMH multi-site study will be developed during the first year of the study.

Mrs. LOWEY. Dr. Shulman.

Dr. SHULMAN. Yes.

LYME DISEASE

Mrs. LOWEY. In my part of the country we have had an incredible expansion of Lyme disease. The incidence of Lyme disease just keeps increasing and people and support groups come in to see me.

And as you know, many of the victims have had tremendous skeletal discomfort, pain, symptoms resembling arthritis.

I would be interested in hearing about your work concerning Lyme disease and those symptoms. Can you give us some understanding of the impact of the budget on your work in this area?

Dr. SHULMAN. Well, let me first discuss the whole question of late-occurring disease in Lyme disease, specifically the late-occurring, chronic arthritis, usually of one or two large joints, such as the knee. We have had a remarkable discovery this year. We put out a request for applications three years ago on Lyme disease and we received a fine response to that. Two such grants led to this discovery.

A wonderful report, which appeared in the "New England Journal of Medicine" on January 27th of this year, concerns a finding using the polymerase chain reaction, which is this wonderful chain reaction, for which I believe the Nobel Prize was awarded last year. Using this reaction, scientists are able to take tiny amounts of material and then multiply it a million times in order to be able to detect small amounts of material.

The big question in terms of late Lyme disease is, whether or not the Lyme disease organism, borrelia burgdorferi, is still there. What this report showed was that the researchers were able to detect the bacteria by this PCR reaction in a remarkable number of patients and with a great deal of accuracy. This allows us, for the first time, to give a precise diagnosis and to see whether the late-occurring arthritis which occurs after early antibiotic treatment is due to the persistence of the bacteria, or whether it is due to some other immunologic process that is going on.

It is really outstanding work. Now we need to build on this discovery by carrying out clinical trials to determine whether the type of treatment for those who still have the Lyme organism should also be applied to those who have an arthritis which may have a different immunologic basis.

Mrs. LOWEY. Thank you very much. I appreciate that response and I look forward to working with you.

Thank you, Mr. Chairman.

Mr. SMITH [presiding]. Mr. Porter, do you have any further questions?

VASCULAR STUDIES

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Hodes, this is a Helen Bentley question. She asked if I would ask it for her since she could not be here this afternoon.

Last year for the NIA, this subcommittee included an increase to establish a laboratory of vascular studies within the intramural program at your Gerontology Research Center to provide information on age-related molecular biology of blood vessels.

What is the status of this laboratory? Can you tell us what kind of priority NIA is placing on this laboratory?

Dr. HODES. Certainly. This laboratory within the Intramural Gerontologic Research Center in Baltimore is an extremely high priority of the Institute. It, under Dr. Lakatta's leadership, is looking at a number of aspects of the cardiovascular system with age and making observations that have the potential to bear heavily in future behavioral and biological interventions to both prevent and treat cardiovascular disease.

As you know, coupled with the language encouraging the Institute to establish and expand research in this intramural area, was a cap put on the overall intramural budget. We have attempted to comply with the priorities suggested by Congress in the context of the overall cap and this laboratory has received preferential allocation of resources within the diminished resources available to the intramural program.

I think that is how I can best and most frankly describe our ability to comply.

Mr. PORTER. Thank you.

Dr. Shulman, the NIAMS is a relatively new Institute. It has never been fully funded compared to sister Institutes. Because we tend to treat each Institute equally in terms of percentage increase, you have never been able to catch up with the others. For instance, your award rate is only 19 percent.

How would you define equity and how much additional funding would you require to achieve equity with other Institutes?

Dr. SHULMAN. I can only say that we do our best with what we have, and we are grateful for that. We have a lot of great unfunded science that could be accomplished with more support. I think I will leave it there.

FIBROMYALGIA RESEARCH

Mr. PORTER. Okay. Can you tell us what is the status of fibromyalgia research at the Institute?

Dr. SHULMAN. Yes, sir. Fibromyalgia, for those of you who may not know, is a disorder characterized by weakness and pain generally occurring in middle-aged women; 85 percent of the people who have it are women. It is a much more common disease than we fully appreciate. It is characterized by general pain all over but more specifically, by having specific tender points. According to criteria that have been developed by the American College of Rheumatology, if you have 11 or more tender points out of 18 areas, then you can qualify as having this disorder. Fibromyalgia is characterized by sleep disturbances.

We organized a symposium that was held in May of 1993, which brought in experts from around the country to discuss what ought to be done. It was a good conference. We then issued a request for applications (RFA) for more research in this area. In response we received 18 new applications.

We intend to fund four to five applications after they are reviewed.

We have some new data that would indicate that perhaps fibromyalgia is more common than rheumatoid arthritis, so it is a very significant disorder in terms of the effect it has in the community. We are looking for basic research in the area of neuroscience as an approach to better understanding and treating this disease.

JOINT REPLACEMENTS

Mr. PORTER. The number of total joint replacements continues to increase. These replacements often provide dramatic improvements in the quality of life. However, after 10 years or so in use, many replacements require some revision surgery due to wear and tear.

What is the Institute doing to develop better long term results with joint replacements?

Dr. SHULMAN. Mr. Porter, you are absolutely correct. We have the old cemented procedures and then we have newer cementless procedures that have been developed by our orthopaedic leaders and those are out there and are doing pretty well for the community, but they do wear out. And so we support research on why they wear out. We have just issued an interactive research grant announcement asking for more research in the area of orthopaedic biomaterials. We are asking groups to get together to develop orthopaedic materials which are better than the ones we currently have.

We also are organizing a Consensus Development Conference on Total Joint Replacements to take place at the NIH September 12th through the 14th of this year.

Mr. PORTER. It is kind of fascinating, as people live longer even if you replace a joint, they outlive the joint, you have to replace it again or make corrections. It is fascinating.

Dr. SHULMAN. It is remarkable to see people with two knee joints go out on the dance floor and do well.

Mr. PORTER. Great.

Looking at the other side of savings from health care reform, it seems to me back pain is one of the reasons for lost work time in this country. Maybe one of the top reasons.

I wonder if you could describe what role stress plays in respect to back pain and what implications that has for treatment?

Dr. SHULMAN. Well, back pain is a big problem. I think we discussed that last year, Mr. Porter.

Mr. PORTER. I know.

Dr. SHULMAN. I am glad to see you are doing so well. I saw you walking in the hall, and you seem to be doing very, very well indeed.

Mr. PORTER. We get all our free medical advice here.

Dr. SHULMAN. I think we need much more research on the pathogenesis of the pain. We need to do more in the area of neuroscience. We are actually exploring this area, and in our efforts to expand research, we have invited leaders to come together at a conference to look at this.

In the area of stress specifically, I think that perhaps stress has something to do with the persistence of back pain, but we don't have good data to suggest that stress really is the initial trigger of the back pain.

Mr. PORTER. Thank you.

HEALTH AND RETIREMENT

Dr. Hodes, what are your plans for continuing the Health and Retirement Study and the Asset and Health Dynamic of the Oldest survey?

Dr. HODES. These are really historic studies which recently have completed their initiation phase and in which large populations have been characterized in terms of economics, health and the interrelationship between those two factors as they relate to the life event of retirement. Plans now involve the longitudinal study of these populations, which is the initial intent and design of the study, to see what happens over these next few years in cohorts of study populations.

A real challenge for the Institute in terms of resource allocation and a very exciting opportunity now centers around the evaluation and analysis of the data that come from these studies. Following the completion of the initial surveys and their longitudinal sequelae, substantial decisions about data analysis will have to be made; the resources required to support such studies will be similarly quite extensive.

We have recently completed the funding of the first Centers for Demography Research. These centers are a little different from the physical centers we are more used to in clinical and physical sciences. Since these demography centers deal with data, they are going to be focused upon multi-institutional collaborative efforts to deal with large bodies of demographic data. The database will be easily accessible through electronic media for consumption by other researchers and policy analysts.

Mr. PORTER. Thank you very much.

Dr. Snow, please bring us up to date on the scope of tinnitus and the status of your research on this disorder.

TINNITUS RESEARCH

Dr. SNOW. Mr. Porter, as you know, tinnitus is a symptom that results from any disease or disorder anywhere in the auditory system and therefore all of the research in our hearing portfolio may turn up information that is important in the answer to the problem of tinnitus.

It is a very common problem; 15 to 20 million Americans have tinnitus. It varies in severity as far as how distracting it is. We have a number of specific studies of the symptom itself. We are developing a database of the characteristics or the profile of individuals who have tinnitus.

Perhaps one of the most important breakthroughs that has occurred in tinnitus research is the evidence that by manipulating the calcium level in the inner ear one can alter the perception of tinnitus. An animal model has been developed for the study of tinnitus, and it is possible by altering the calcium level systemically or by the use of calcium channel blockers in the inner ear to eliminate the tinnitus. This research is not at the stage in which we can go forward with a clinical trial, but perhaps soon we will have therapeutic strategies that merit large-scale clinical trials.

We are going to hold a conference in fiscal year 1995 on tinnitus to bring together individuals both who have a reputation for research in that area as well as individuals who have not specialized in tinnitus in their research to examine the state-of-the-art of the field and to recommend strategies for both a short-term and long-term plan for addressing this problem.

HEARING AID RESEARCH

Mr. PORTER. Did you tell us you have got a collaboration going with the Department of Veterans Affairs on hearing aid research and development?

Dr. SNOW. Yes.

Mr. PORTER. Can you tell us about the status of that?

Dr. SNOW. That is coming along very well. One program announcement on the understanding of speech with amplification in quiet and in noise has been published. Another program announcement on the benefit of amplification for hearing-impaired persons is about to be released. A request for proposals for device development will be issued soon. The planning for the clinical trial is on schedule. The protocol writing committee has developed a splendid protocol that is being finalized.

We hope to start that clinical trial in September of this year. And we are planning the first of the biennial conferences in September of 1995. So we have made good progress. Everything that has been planned is on schedule.

Mr. PORTER. Thank you.

EATING DISORDERS

Dr. Cowdry, I understand you may have discussed this while I was in another meeting, but during the last two years, this Committee has directed NIMH to conduct a public and professional education campaign on eating disorders.

What is the status of that effort?

Dr. COWDRY. Mr. Porter, one of the more interesting things as I have taken this job is following issues such as this question of the eating disorders campaign and trying to get up to date on where we stand with that.

Reviewing the results of the May 1993 conference that was held in Chicago and its recommendations, and trying to decide what our response to those recommendations should be—I did discuss that a bit earlier.

Let me focus specifically on issues of how we can collaborate with the McKnight Foundation which has just funded a $4.6 million proposal that includes preparation of some materials for public education.

I think that there are opportunities for collaboration in that area. I will tell you that another thing that we are doing is evaluating our public education campaigns generally. Clearly, there was a better database for providing an extensive public and professional education campaign in depression, which we did with the Depression: Awareness and Recognition and Treatment campaign, which is underway and remains very active; and secondly, in the current panic disorders campaign.

I think that in this time of decreasing resources we need to ask ourselves how we can carry on a broader spectrum of professional education including eating disorders. I have not yet reached a decision about how to move forward with that and will be happy to report that to you in the coming year. I realize this is yet another promise, but I will do so.

Mr. PORTER. Thank you.

RHEUMATOID ARTHRITIS

A final question for Dr. Shulman and this is one that a constituent wanted me to ask you.

The minocycline trial on the treatment of rheumatoid arthritis has shown positive results. What additional studies must be conducted before the antibiotic treatment of rheumatoid arthritis is widely accepted and practiced?

Dr. SHULMAN. The trial that you refer to is a six-center trial with minocycline, well controlled by a placebo group carried out over a 48-week period. That trial showed moderate benefit and low toxicity to the patients treated with the drug.

In terms of rheumatoid arthritis, there is another trial that is also being published. This material will soon be published in the literature.

I don't know what the official recognition requirements would be with respect to this particular agent being used for rheumatoid arthritis. I don't know whether it might in fact be allowable to use it now. In terms of an individual constituent, it would be up to the person's physician to make a judgment on what the best treatment is for that person.

Mr. PORTER. Thank you.

Thank you all very much.

Thank you, Mr. Chairman.

BACK PAIN

Mr. SMITH. Dr. Shulman, I just had one more question. Back problems related to the nerve touching the skeleton, the bone, what is the current most popular kind of operation for that or the one that causes difficulty the least often.

Dr. SHULMAN. What is the best operation for a back problem?

Ms. PELOSI. Exercise.

Mr. SMITH. Where the nerve touches the bone.

Dr. SHULMAN. A second opinion is the best operation.

Mr. SMITH. It changes about every year.

Dr. SHULMAN. I think, to be quite serious about this, that Ms. Pelosi has really touched on the right answer and that is that people used to go to bed quickly and were told to get a lot of rest when the acute back pain appeared.

There are good data indicating that this is not the best approach, that trying to get up and get around, as Mr. Porter knows, is just the right thing to do.

The place and role of back surgery and the many types of back surgery depend on the individual. I think that surgery can often be effective but I think it has to be tailored for the individual person, Mr. Chairman.

Mr. SMITH. Well, I used to have a lot of workmen's comp cases and I remember there was a period there when someone developed a process of putting a screw in between the joints to lift them apart. It worked great for a while until all at once somebody dies on the operating table so they quit that. And then for a while they were welding them together. They are not doing either one of those any more; are they?

Dr. SHULMAN. No, sir. I imagine somebody may be doing it, but that is not the common practice.

Mr. SMITH. Somebody comes along every once in a while and thinks they finally found the answer to this. There is no answer to it; is there?

Dr. SHULMAN. In terms of workmen's compensation, there has been some very interesting research, prize winning research, done by Dr. Stanley Bigos in Washington state. He did a major study at the Boeing plant and found that dissatisfaction with one's work is a very important contribution to chronic back pain. You may not find this surprising, but with this research, we have facts to back up what many of us have suspected for some time. This relates to our earlier discussion of stress and lower back pain.

Mr. SMITH. Well, that may be true in some cases, but I have to—I don't like to do this but I will refer to a personal experience I had. There was a doctor—I won't use his name—who was on the witness stand and he was telling me that the best cure was dollar bills, greenbacks. And I said, isn't that the same cure that you prescribed about a month ago for a fellow that died two days later?

Dr. SHULMAN. Well, as I have said I think that spine surgery is an important tool, but should be tailored for each individual.

Mr. SMITH. It is a very serious problem. A lot of people make fun of it because they don't know how serious it is when it is somebody else's back.

Dr. SHULMAN. I could not agree with you more. I have a back problem myself, and I disagree with the notion we used to have that back pains often indicated emotional problems. I am not saying that. I am saying that perhaps the persistence of the pain, not the induction of the pain, may in some way, according to recent studies, have something to do with the stress in people's lives.

Mr. SMITH. But it comes and goes; doesn't it? They can be all right for a while and then get it back?

Dr. SHULMAN. Yes, sir. I have had back problems since I was a teenager, and it does come and go.

Mr. SMITH. So the answer is don't operate unless you just can't get along with it?

Dr. SHULMAN. That is correct.

Mr. SMITH. That is all.

Dr. SHULMAN. Thank you very much.

Mr. SMITH. Thank you.

We will have another panel.

Dr. VARMUS. Thank you.

[The following questions were submitted to be answered for the record:]

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

ALLOCATION OF FUNDS BY DISEASE

Mr. Smith. The Committee has heard from groups challenging the way funds are allocated among diseases at your Institute. They contend that funding should be more closely related to the number of people affected, so that, for example, osteoarthritis research would receive more money. How would you respond to these criticisms?

Dr. Shulman. The NIAMS was established in 1986 with a mandate from Congress to conduct and support research and training in arthritis and musculoskeletal and skin diseases. This mandate was recently amended by P.L. 103-43 to include specific attention to research on the effects of these diseases on children. To that end, NIAMS has been, and continues to be, committed to supporting the highest quality of science in the research fields that fall within its research mandate. These include such scientific disciplines as rheumatology, orthopaedics, dermatology, sports medicine, immunology, genetics, molecular and structural biology, and biochemistry and physiology. Like other NIH institutes, NIAMS has operated under the fundamental principle that the primary criterion for supporting a research grant or contract is scientific excellence. The NIAMS has taken special care to follow that principle in providing support for the many investigator-initiated research grants that are submitted to the NIAMS for support from the Institute's five programs: rheumatic diseases; bone biology and bone diseases; musculoskeletal diseases; muscle biology; and skin diseases.

When making decisions on what areas in which to issue institute-specific initiatives, NIAMS considers the scientific opportunities as well as the public health impact of a particular disease. It is important to note that scientific opportunity does not always follow frequency of a particular disease. For example, through advances in molecular research we have seen tremendous advances in understanding the genetic defects underlying several forms of the devastating skin disease epidermolysis bullosa (EB). While EB may be considered a rare disease (200,000 people or less), it is a serious disease with numerous complications and can result in death for those affected. Continued support over the past several years for research on this disease has been critical for the advances that have been made to date.

With respect to research on osteoarthritis, NIAMS is committed to enhancing support for research on this disease, the most common of all arthritic diseases affecting an estimated 16 million Americans. From a public health standpoint, this is a costly disease. In addition, there are scientific opportunities to explore. In April, NIAMS, in collaboration with the American Academy of Orthopaedic Surgeons, sponsored a scientific workshop to review the current state-of-knowledge of research on this disease and to develop recommendations for future research directions. The Institute will consider these recommendations when developing plans for future institute-initiated announcements. In September, NIAMS will co-sponsor a consensus development conference on total joint replacement, and the Institute has issued an announcement inviting research on new orthopaedic materials for the development of improved and longer lasting orthopaedic devices. These efforts should help to stimulate the scientific community to submit new and innovative research proposals on osteoarthritis.

RESEARCH CENTERS

Mr. Smith. Given your low success rate, has Congress made a mistake in encouraging you to use your scarce resources to establish new centers, such as the recent exploratory center in juvenile rheumatic diseases?

Dr. Shulman. The NIAMS does have a low success rate in comparison to other NIH institutes and the NIH average. This low success rate is a result of the availability of resources combined with the number of excellent research grants that are submitted to this Institute. There is a tremendous amount of scientific opportunity in the fields that fall within the NIAMS research mandate.

The establishment of an exploratory research center in juvenile rheumatic diseases, while encouraged by the Congress in FY 1993, was an appropriate institute-initiated program. Research on rheumatic diseases in children is a scientific area that can benefit by the multidisciplinary research opportunities that are provided by the center mechanism. At present, there are very few pediatric rheumatology researchers available to conduct research investigations. Establishment of an exploratory center will enhance the research base and allow the investigators the opportunity to develop preliminary data sufficient to provide the basis for applications for independent research grants. In addition, it is important to note that this award for the juvenile research center underwent the standard NIH two step-peer review process and was awarded based on its scientific excellence.

INTRAMURAL RESEARCH PROGRAM

Mr. Smith. Because you are a young institute, you have not established an extensive intramural research program. With the staffing constraints facing NIH, are you evaluating whether you should forego further development of an intramural program?

Dr. Shulman. Given the current staffing constraints facing NIAMS, we have had to evaluate our staffing priorities for all areas of the Institute to determine the best possible use of our limited resources. We believe that the best approach to adapting to these staffing constraints is to maximize our efficiency, rather than to eliminate or reduce useful programs. NIAMS has worked hard to establish high caliber Intramural and Extramural Research Programs. Our Intramural Program consists of a group of stellar scientists who are recognized as leaders in their fields both nationally and internationally. The Institute's Intramural Program has received praise and support from researchers in the extramural community. For these reasons, we feel that it is appropriate for

NIAMS to continue working within our constraints to develop our Intramural Program to the level originally proposed and planned when the Institute was created.

DISEASE REGISTRIES

Mr. Smith. Tell us more about your approach to the requests from many disease groups for patient registries? How many registries to you plan to support with the funds you have set aside?

Dr. Shulman. Over the past several years NIAMS has been approached by a number of patient advocacy groups and members of the research community to consider development of patient registries for rare diseases, specifically heritable diseases of connective tissue and skin diseases, such as the ichthyoses. Congress has also expressed an interest in this area.

In response to this interest, in February 1994, NIAMS issued a Broad Agency Announcement (BAA) inviting applications for establishment of research registries for rare diseases. The announcement includes all program areas within NIAMS, including specific heritable disorders of connective tissue and skin diseases such as the ichthyoses. The application receipt date was April 12, 1994. NIAMS anticipates funding two to three five-year contracts.

FUNDING FOR DISEASES

Mr. Smith. Identify projected 1993-1995 spending for the following: osteoporosis, rheumatoid arthritis, osteoarthritis, lupus, Lyme disease, epidermolysis bullosa, ichthyosis, psoriasis, alopecia, scleroderma, osteogenesis imperfecta, Marfan syndrome, and fibromyalgia.

Dr. Shulman. Funding for these diseases in FYs 1993-1995 is as follows:

	FY 1993 actual	FY 1994 estimate	FY 1995 estimate
Osteoporosis	$42,148,000	$46,174,000	$48,077,000
Rheumatoid Arthritis	16,130,000	17,491,000	18,265,000
Osteoarthritis	11,626,000	12,350,000	13,063,000
Lupus	16,411,000	17,698,000	18,329,000
Lyme disease	2,977,000	3,112,000	3,240,000
Epidermolysis bullosa	6,487,000	7,089,000	7,490,000
Ichthyosis	4,152,000	4,329,000	4,485,000
Psoriasis	2,501,000	2,868,000	2,999,000
Alopecia	402,000	419,000	436,000
Scleroderma	2,079,000	2,177,000	2,964,000
Osteogenesis imperfecta	2,641,000	2,750,000	2,862,000
Marfan syndrome	1,420,000	1,477,000	1,532,000
Fibromyalgia	424,000	1,865,000	1,941,000

RESEARCH CENTERS

Mr. Smith. Identify the number, type and subject matter of research centers supported in 1994.

Dr. Shulman. The NIAMS plans to support 30 research centers in FY 1994. These include 14 Multipurpose Arthritis and Musculoskeletal Diseases Centers, 9 Specialized Centers for Research (SCORs), 6 Skin Disease Research Core Centers, and 1 Juvenile Rheumatic Diseases Research Center Planning Grant. Included in the nine SCORs are 4 in rheumatoid arthritis, 1 in osteoarthritis, 2 in osteoporosis, and 2 in systemic lupus erythematosus (SLE).

LOW BACK PAIN

Mr. Smith. We have heard that more people see doctors for back pain than for any other medical ailment except colds and upper respiratory complaints, often because they did not use the proper methods of lifting and moving an object.

Doctor, what efforts are you or other agencies of the Public Health Service undertaking to educate the population regarding activities, specifically high risk activities away from the workplace, that jeopardize their backs? For example, family caregivers are at great risk when transferring a loved one from the bed to a chair or pulling a person who is reclining in bed into a sitting position.

Dr. Shulman. NIAMS has assembled, distributed, and recently updated a public information packet on low back pain. The packet includes general information on the back and on back problems, as well as information on prevention and exercise, and the treatment and management of low back pain. In addition, the Institute provides speakers to give presentations to local lay organizations on the topic of musculoskeletal injuries, including back problems. We also respond to inquiries from the public about low back pain.

As a result of a 1988 scientific workshop on low back pain research, a book entitled "New Perspectives on Low Back Pain" has been published which includes an introduction by the Chief of the NIAMS Musculoskeletal Diseases Branch. The Institute is currently in the process of planning another workshop on three common aspects of low back pain to stimulate more interest in research on this subject. The hope is that information gained from this workshop will filter into information directed toward educating the public. Through this workshop, NIAMS also plans to address some practical questions most often asked by patients of their doctors. The Institute previously utilized this same format in a workshop on sports and exercise in mid-life, and we hope to publish the questions and answers in an effort to increase public awareness.

Mr. Smith. What research is currently being conducted to develop more accurate diagnostic procedures for back pain? Also, are you looking at how to treat this problem with non-operative treatments instead of surgical procedures?

Dr. Shulman. NIAMS supports research on the prevention, diagnosis, treatment, and causes of back pain. One Institute-supported researcher is studying ways to improve the usefulness of three different techniques in diagnosing back pain. Other researchers are working to develop better diagnostic techniques and objective guidelines for the treatment of back injuries. In terms of treatment, researchers are studying different surgical procedures to assess how effective and appropriate they may be. Researchers are also working to identify risk factors for back problems, and to develop rational and effective preventive and therapeutic approaches to back pain. To stimulate more research in these areas, the Institute is planning to sponsor a workshop on three common aspects of low back pain.

RHEUMATOID ARTHRITIS

Mr. Porter. More than 2 million Americans, mostly women, are affected by rheumatoid arthritis. What can you tell us about recent advances in this area?

Dr. Shulman. One of the most promising advances in rheumatoid arthritis this year is the finding that the improvement of arthritis during pregnancy is related to how a mother and unborn child differ genetically. NIAMS researchers found that a particular set of genetic markers, known as human leukocyte antigen (HLA) genes, were more frequently dissimilar between mother and child in the 75 percent of the pregnancies where the disease improved. Researchers now believe that genetic differences between the mother and child may set off maternal immune responses that lessen the symptoms of arthritis in the mother during pregnancy. This finding provides an intriguing new focus for uncovering causes of remission in rheumatoid arthritis.

In previous studies with animals, NIAMS intramural scientists showed that development of rheumatoid arthritis involves defects in the complex nervous system-hormone (neuroendocrine) network that controls the body's response to inflammatory stimuli and other stresses. They have now found a hormone in humans suffering from rheumatoid arthritis that may carry signals between the neuroendocrine and inflammatory systems. The researchers are comparing neuroendocrine responses in rheumatoid arthritis patients and normal individuals in hopes of demonstrating that abnormal interactions among the nervous, immune, and hormone systems predispose individuals to disease. If this hypothesis is proved, it could lead to development of new preventive strategies.

FIBROMYALGIA

Mr. Porter. Dr. Shulman, I was pleased that you issued an RFA on fibromyalgia. Do you generally allow only two months for a response to RFAs, as you did in this instance, and what was the response to the RFA?

Dr. Shulman. Following the workshop on fibromyalgia that the Institute held in May 1993, NIAMS issued a Request for Applications (RFA) for basic research on fibromyalgia. The announcement was published October 29, 1993. The letter of intent receipt date was December 15, 1993, and the application receipt date was February 10, 1994, giving applicants 15 weeks to respond to the RFA. The dates for receipt of RFAs are chosen according to a variety of criteria, including the availability of personnel to handle and to review the applications. In this case, the Institute followed its usual procedures for setting dates; three months from publication to receipt is our average. NIAMS is very pleased with the 18 responses we got to the RFA on fibromyalgia, especially since there is not an abundance of researchers in this area.

JOINT REPLACEMENT

Mr. Porter. What steps has your institute taken to insure that sufficient funds are committed to research to achieve better long-term results of joint replacement?

Dr. Shulman. Orthopaedic joint implants are very commonly used in the treatment of musculoskeletal diseases and injuries. In 1992, there were an estimated 400,000 joint replacements performed on knees or hips. It is estimated that approximately 5 million people in the U.S. currently have an orthopaedic device implanted. These orthopaedic devices have had great general success in reducing the morbidity and disability that may result from musculoskeletal diseases. To further research in this area, in October 1993, NIAMS issued an RFA inviting Interactive Research Grant Applications on new orthopaedic biomaterials for the development of improved and longer lasting orthopaedic devices. We intend to make an award in the fall of 1994. Also, NIAMS, in collaboration with the NIH Office of Medical Research Applications, will hold in the fall of 1994 a consensus development conference on total joint replacement.

OSTEOARTHRITIS

Mr. Porter. What plans do you have for follow-up of the basic and clinical research identified at your recent workshop on osteoarthritis? Will sufficient funds be available to carry out this research?

Dr. Shulman. On April 23-26, 1994, NIAMS, in collaboration with the American Academy of Orthopaedic Surgeons, sponsored a scientific workshop entitled, "New Horizons in Osteoarthritis." Researchers from across the country and abroad participated in this successful four day conference that was designed to provide a forum to increase the exchange of scientific ideas among an interdisciplinary group of scientists, including orthopaedic surgeons, rheumatologists, epidemiologists, and bioengineers. Participants summarized the current state of knowledge in both basic and clinical research and identified future directions for research on this chronic disease. NIAMS will consider the recommendations from the workshop to develop an institute-initiated announcement to invite new research applications on this disease. Sufficient funds will be available to support highly meritorious research on this disease.

Mr. Porter. For the record please summarize the major recommendations of this workshop.

Dr. Shulman. Members of the American Academy of Orthopaedic Surgeons who were on the planning committee for this workshop are preparing the written recommendations from this workshop. As soon as we receive a copy of these recommendations, we will be happy to forward them to your attention. In addition, the planning committee in collaboration with NIAMS staff plan to publish a book based on this workshop.

RHEUMATOID ARTHRITIS

Mr. Porter. Have the results of the NIAMS-supported minocycline trial on treatment of rheumatoid arthritis been published, and will there be a public announcement of the results by the Institute?

Dr. Shulman. The results of the NIAMS-supported minocycline trial show that the antibiotic has some benefit for treating rheumatoid arthritis. These results were announced publicly at the American College of Rheumatology meeting in San Antonio, Texas, in November 1993, and a manuscript has been submitted for publication. How effective minocycline is compared to other treatments for rheumatoid arthritis remains to be determined.

FIBROMYALGIA

Mr. Porter. Your Institute is to be commended for approving a $1.4 million RFA for fibromyalgia syndrome (FMS).

How would you grade the response you received from the RFA?

Do you feel that a higher response might have been achieved had the researchers been given more than two months to prepare their applications?

Dr. Shulman. Given the relatively recent publication of classification criteria for fibromyalgia, we are excited about the 18 responses that we received to our Request for Applications (RFA). The RFA was issued October 29, 1993, with a receipt date of February 10, 1994, allowing applicants a period of 15 weeks to prepare and submit proposals. This period of time is consistent with the Institute's average of three months between publication of an RFA and receipt date. The $1.4 million will fund research that will be invaluable in providing a better understanding of the pathogenesis of what can be a chronic and disabling condition.

Mr. Porter. Researchers in the field of FMS claim that the approval of an R01 application on FMS by your Institute is either extremely rare or it has never been done before.

Could you shed more light on this matter?

It is anticipated that many applicants responding to the RFA for FMS research will not be approved due to financial limitations (only 5 grants will be awarded). Traditional advice to applicants might be to "rework and resubmit as an R01." Given your Institute's past history for R01s and FMS projects, what encouragement, if any, can you offer these investigators?

Dr. Shulman. A major reason for the lack of funded R01s studying fibromyalgia has been the lack of applications submitted in this area. For fibromyalgia applications to achieve a higher approval rate, NIAMS must receive a sufficient number of grants, and those grants must be of high scientific quality.

To stimulate research in this field, the NIAMS held a workshop in May 1993 on the current status and future directions of fibromyalgia research. Following the workshop, the Institute issued a Request for Applications (RFA) inviting applications for basic research on the pathogenesis of fibromyalgia. As a result of this RFA, NIAMS expects to fund five to seven new awards.

If the Institute receives a large number of meritorious applications in response to this RFA, we would encourage unfunded investigators to amend and resubmit their applications as R01s. Since these applications will have already been reviewed once, they may have a better chance of being competitively successful. This has been the case with some previous RFAs issued by the Institute, such as our RFA on Basic Research in Osteoporosis. This RFA, issued in 1991, generated a number of amended applications which successfully competed as R01s.

OSTEOPOROSIS

Mr. Stokes. Osteoporosis is truly a disease that disproportionately affects women to say the least. How many of the more than 25 million Americans that suffer from this disease are women, and of that number how many are African American women? Doctor, are we really making progress in treating and preventing this disease? How extensive are the clinical trials that you have underway in this area? To what extent are African Americans participating in these trials?

Dr. Shulman. Of the 25 million Americans who suffer from osteoporosis, more than 18 million are women. It is known that osteoporosis is found less often in African American women than in white women, and the Women's Health Initiative will include a series of bone density studies conducted by three centers in which minorities will figure prominently in order to establish a precise figure. Two of the centers have enrolled at least 60 percent minorities, and one is focusing on African Americans.

We are making significant progress in treating and preventing osteoporosis. Researchers have found a gene that may help identify, early in life, individuals who are at risk for the disease, and three factors have been found to affect the building of maximum bone in women during adolescence and early womanhood: calcium intake, physical activity, and oral contraception. Other studies indicate that inhibiting the production of interleukin-6 may be an important factor in regulating the excess resorption of bone by osteoclasts. Three highly promising treatments for osteoporosis are under investigation: alendronate, raloxifene, and pulsed parathyroid hormone. The Institute is planning to sponsor a consensus development conference on optimal calcium intake for maximum bone development.

In terms of clinical trials, Institute staff members are actively involved with the research efforts of the Women's Health Initiative and the Postmenopausal Estrogen/Progestin Intervention Trial. The Institute supports 19 clinical trials currently; of the 19, 13 deal with osteoporosis. Since its program announcement in the NIH Guide for Grants and Contracts in May 1987, NIAMS has fully complied with the special instructions for inclusion of women and minorities in clinical research studies.

LUPUS

Mr. Stokes. Lupus is three times more prevalent in African American Women than in their white counterparts. What progress are you making and what research initiatives are underway to accelerate advances in the treatment and prevention of this autoimmune disease? To what extent is there a collaborative effort with the National Institute of Allergy and Infectious Diseases on research that would expedite research advances in lupus?

Dr. Shulman. Although the cause of lupus is not completely understood, the disease is believed to result from an interplay of genetic, environmental and hormonal factors. An exciting new avenue of research indicates that lupus may involve defects in a process by which the body eliminates unnecessary, damaged, or potentially harmful cells. This process is known as programmed cell death or apoptosis. In the immune system, apoptosis is responsible for eliminating white blood cells with the potential to react against the body's own tissues. Normally, the immune system detects these "self-reactive" cells, and they are destroyed by apoptosis before they do any harm. If the process of apoptosis is defective, self-reactive cells will survive and may cause autoimmune diseases such as lupus. Researchers have found that replacing a single defective gene can correct a lupus-like autoimmune disease in mice. The gene, called *lpr* or *fas*, plays a key role in this process known as apoptosis. This research is very exciting and may open the door to new treatments targeted to specific defects in lupus.

I am also pleased to report to you that as a result of the Requests For Applications issued in 1993, NIAMS is supporting 15 new basic research grants in lupus, including three population studies that specifically search for the causes of the high prevalence of lupus among African American women. We will continue to monitor the progress of these grants and develop new Institute-initiated activities as appropriate.

The NIAMS Task Force on Lupus in High Risk Populations has updated its brochure "What Black Women Should Know About Lupus" and created a Community Program Kit with guidelines for developing community awareness programs. NIAMS staff and the Task Force are working actively with the United Methodist Church of the greater Baltimore Washington Area to implement community-based public education programs on lupus. Other Task Force plans include the development of continuing medical education programs for physicians via the National Medical Association.

NIAMS and the National Institute of Allergy and Infectious Diseases (NIAID) collaborate in a variety of ways on lupus research. The NIAID is funding a number of research grants as a result of the RFA issued in 1993 on causal mechanisms of lupus. In addition, NIAMS and NIAID together issued two other RFAs in 1993 inviting applications for program project grants on autoimmunity and research applications to investigate mechanisms of oral tolerization and immunization. We will continue to work with the NIAID to further research on lupus.

ARTHRITIS IN CHILDREN

Mr. Stokes. How extensive is the problem of arthritis in children? What is the most important research that is underway to relieve their suffering and to prevent this disease?

Dr. Shulman. It is estimated that more than 200,000 children in the United States suffer from one or another form of arthritis or rheumatic disease. About 70,000 have the juvenile form of rheumatoid arthritis (JRA), which may cause pain, swelling, and limited motion in one or more joints, as well as inflammation in other parts of the body, such as the eye. Children can develop other rheumatic diseases as well, including systemic lupus erythematosus, dermatomyositis (an inflammation of skin and muscle), and Kawasaki disease (an inflammation of the blood vessels). Rheumatic diseases in children pose a diverse set of challenges to patients and their families, physicians, and researchers. In September 1993, NIAMS awarded a grant for the establishment of a Juvenile Rheumatic Diseases Research Center to support the expansion of multidisciplinary research on the causes of rheumatic diseases in children and the development of new treatment strategies. Scientists at the Center will investigate the genetic basis, causes of inflammation, and the role of bacteria and viruses as triggers of these diseases.

Also in September of 1993, NIAMS held a highly productive scientific workshop on basic and clinical research for the several rheumatic diseases of children. NIAMS will issue a Request for Applications (RFA), based on the recommendations from this workshop. New research that will result from this RFA and the work at the Juvenile Rheumatic Diseases Research Center will be very important in expanding the field of pediatric rheumatology research and in addressing the many diverse issues facing both pediatric clinicians and investigators who are concerned with these diseases.

SPINAL ARTHRITIS

Mr. Stokes. To what extent will the Institute be able to pursue the research challenges in spinal arthritis at the FY 1995 budget level?

Dr. Shulman. As I reported in my opening statement at the hearing we are seeing great progress in the area of spinal arthritis. Three years ago, researchers discovered that when the human gene HLA-B27 (a gene that is found in over 90 percent of the patients with spinal arthritis), was injected into rats, these transgenic rats developed not only arthritis of the spine and joints, but also skin and nail lesions of psoriasis and Reiter's disease, both associated with spinal arthritis. This year the same study was performed using HLA-B27 transgenic rats that were bred in a germ free environment. These germ-free rats developed the skin and nail changes, but they did not develop the arthritis that was observed in animals raised in a normal environment. This research proves that the HLA-B27 gene alone cannot induce the arthritis--an infectious agent must be present. This is very exciting research and NIAMS will continue to support meritorious applications submitted to the Institute on this research topic.

NUTRITION

Mr. Stokes. Today we are learning more and more about the direct relationship between nutrition and disease prevention. How extensive is the research in this area at your institute? Is that research geared toward a specific disease or for the advancement of disease knowledge in general, explain.

Dr. Shulman. The Institute supports 36 nutrition grants related to arthritis and musculoskeletal and skin diseases. Most of them (27) focus on nutritional factors that influence metabolism in the musculoskeletal system, six concern the influence of various vitamins (and hormones) on skin maturation, and three focus on the role of dietary factors in immune and inflammatory responses.

Among the grants related to the musculoskeletal system are three dealing specifically with the prevention and management of osteoporosis. Researchers are attempting to determine the optimal level and form of calcium that should be consumed at different stages of life in order to build and maintain strong bones. Related to this research is the NIH Consensus Development Conference on dietary calcium that NIAMS is cosponsoring June 6, 7, and 8, 1994.

MOLECULAR BIOLOGY

Mr. Stokes. Can you highlight for us what advances could stem from increased investments in molecular biology, as it relates to the diseases and disorders under the purview of your institute?

Dr. Shulman. Using molecular biology techniques, NIAMS-supported investigators in Australia recently found a gene that may help to identify, early in life, individuals at high risk for osteoporosis. This gene strongly influences bone density, an important factor in osteoporosis. Increased investments in molecular biology would enable these investigations to be pursued in larger populations in the United States. The results of such investigations could provide an important explanation for the wide variation in bone density, not only among individuals, but also among ethnic groups. They could also pave the way for developing new targeted approaches to the prevention and treatment of osteoporosis.

Future investments in molecular biology in other NIAMS areas could result in:

- Characterization of the genetic components of complex puzzling diseases such as osteoarthritis, osteogenesis imperfecta, and psoriasis;
- Identification of molecular targets for new drug interventions in therapies for autoimmune disorders, including rheumatoid arthritis, lupus, scleroderma, and Sjogren's syndrome; and
- Production, maintenance, and supply of genetically altered animals that mimic human diseases of concern to NIAMS.

GENE THERAPY

Mr. Stokes. Gene Therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly. How much is included in the FY 1995 Budget Request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Shulman. There are a number of diseases and disorders within the NIAMS mandate for which gene therapy offers hope. These include diseases caused by single genetic defects, many of which have been identified in recent research efforts, such as the hereditary skin diseases ichthyosis and epidermolysis bullosa, heritable connective tissue disorders such as Marfan syndrome and osteogenesis imperfecta ("brittle bone disease"), and Duchenne muscular dystrophy, the most common form of childhood muscular dystrophy. There is also great hope for the use of gene therapy to treat diseases with more complex genetic causes, for example psoriasis and the arthritic diseases systemic lupus erythematosus (SLE) and rheumatoid arthritis. Details of the research in a few of these areas are given below.

The recent identification of the specific genetic defects underlying several forms of epidermolysis bullosa, a set of devastating blistering skin diseases, and epidermolytic hyperkeratosis, one of a group of scaling skin diseases known as the ichthyoses, is a major step on the road to treating these diseases by gene therapy. Because the skin is an easily accessible tissue, skin disease researchers believe it is an ideal target for gene therapy. For example, it may be possible to remove skin cells from a patient with a genetic skin disorder, grow the cells in a laboratory dish where the gene defect can be more easily corrected, and then graft the genetically repaired cells back onto the patient's skin. Additional research will be needed to explore the feasibility of this approach as well as other approaches that have been proposed for gene therapy of these and other skin diseases, including albinism and psoriasis.

In an important step toward gene therapy for muscular dystrophy, researchers have discovered a gene therapy technique that prevents mice from developing a condition very similar to Duchenne muscular dystrophy (DMD). By inserting a normal gene for the protein dystrophin into mice that lacked a functioning form of the gene, the researchers were able to ameliorate the defect that causes the muscle degeneration associated with muscular dystrophy. These findings as well as other ongoing research suggest that, in the future, gene therapy for humans with muscular dystrophy may be feasible.

Lupus, like many autoimmune diseases, is believed to involve the concerted action of several genes. However, recent research in mice that develop a lupus-like disease showed that replacing a single, critical defective gene eliminated many of the symptoms of the disease. This and other ongoing research in both mice and humans with lupus indicates that lupus may involve defects in genes that control a process known as programmed cell death or apoptosis. Apoptosis enables the body to eliminate potentially harmful cells such as the white blood cells that can trigger an autoimmune response, in which the body attacks its own tissues. If studies now underway succeed in identifying the critical gene defects that underlie lupus in humans, gene therapy for this disease in humans may well be possible in the future.

Recent research also indicates some promising avenues for pursuing gene therapy for rheumatoid arthritis, a potentially crippling disease of the joints. Studies in animals indicate that it is possible to remove joint cells, insert into these cells a gene that drives production of a protein that reduces inflammation, and then inject the cells back into the joint, where they continue to produce the anti-inflammatory protein. It may also be possible to use specially engineered viruses to carry specific genes to joints throughout the body. These genes might drive production of proteins that block inflammation, and thus decrease joint pain and swelling, or of proteins that promote healing of damaged joint tissues, and thus reduce or prevent deformity due to rheumatoid arthritis. Another direction being explored for gene therapy for rheumatoid arthritis involves targeting the white blood cells involved in the abnormal immune responses believed by many researchers to be an early step in the development of this disease.

By means of gene therapy, proteins that block these aberrant immune responses would be targeted to the white blood cells.

The FY 1995 budget request for NIAMS includes $835,000 for gene therapy research. In FY 1994, NIAMS expects to support $806,000 in gene therapy research. Actual funding for gene therapy research in FY 1993 was $773,000.

MINORITY HEALTH

Mr. Stokes. With regard to diseases and disorders that affect minorities, what are the most significant areas of research that are supported and conducted by your Institute?

Dr. Shulman. Several of the many diseases within the purview of the NIAMS either disproportionately affect minorities or are of special concern to minorities. Among the most significant are lupus, which disproportionately afflicts African Americans; vitiligo, which is especially pronounced in dark-skinned individuals; and spinal arthritis, which disproportionately affects Eskimos and members of the Gila River Indian Community.

Lupus is a serious autoimmune disease that primarily affects young women and is three times more common in African-American women than in white women. Research on lupus is a high priority for the Institute, and we are excited to report that in a recent advance, researchers have found that replacing a single defective gene can correct a lupus-like autoimmune disease in mice. The gene, called *lpr* or *fas*, plays a key role in a process known as programmed cell death or apoptosis. Apoptosis enables the body to eliminate unnecessary, damaged, or potentially harmful cells. This research may open the door to new treatments targeted to specific defects in lupus.

As a result of Requests for Applications (RFAs) issued in FY 1993, NIAMS is supporting 15 new basic research grants in lupus, including three population studies on the causes of the high prevalence of lupus among black women. NIAMS co-funded these grants with the NIH Office of Research on Minority Health (ORMH), and the Institute will continue to work with ORMH to support research on diseases that disproportionately affect minorities.

Vitiligo is another disease of concern to this Institute that affects African Americans. Individuals with this disease develop patches of skin that are devoid of pigment. Although people of all ages, races, and gender can be affected, the disease is especially pronounced in people with darker skin because of the marked contrast between their normal skin color and the lighter patches of vitiligo. NIAMS supports research aimed at determining the genetic and molecular causes of vitiligo, and at developing effective treatments for the disease.

Spinal arthritis is a disease that has been shown to disproportionately affect Eskimos and Pima Indians, and recent research has led to a significant advance in this area. In a study using transgenic rats expressing the human HLA-B27 gene, researchers have discovered that both genetics and infection are needed to cause spinal arthritis. The researchers conducted the same study to determine the cause of spinal arthritis using first transgenic rats bred in a normal environment, and then transgenic rats bred in a completely germ-free environment. The germ-free rats did not develop the joint or bowel inflammation seen in animals exposed to a normal environment, leading researchers to conclude that an infectious agent, along with the HLA-B27 gene, must be present to induce the arthritis.

Mr. Stokes. As the Director of an institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues--while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and--while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Shulman. There are major problems in delivery of and access to health care for minority populations and individuals of lower socioeconomic status. In addition to investing in research that directly affects the health of minorities, the NIAMS has implemented programs to increase awareness within minority populations. One example is the NIAMS Task Force on Lupus in High Risk Populations, which has developed a brochure on "What Black Women Should Know About Lupus" and has created a Community Program Kit that includes guidelines for developing community awareness programs. We believe that continued research, along with improved outreach programs, can have a positive impact on the health of minorities.

RESEARCH TRAINING

Mr. Stokes. For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Shulman. NIAMS is committed to ensuring that a pipeline of properly trained researchers interested in studying arthritis, musculoskeletal, and skin diseases exists. This pipeline exists for many of the research areas supported by NIAMS. In some research areas under the purview of the Institute, however, there is too small a number of researchers that specialize in studying the disease. This has been the case with research on arthritis in children.

To strengthen and expand this pipeline of researchers, NIAMS supports several programs that encourage and support individuals at all levels to pursue a career in biomedical research. In addition to funding a number of individual and institutional research training grants for predoctoral and postdoctoral scientists, the Institute is also involved in programs to support science education in high schools and colleges. As a participant in the Adopt-A-School Program, the Institute developed an agreement with Wilson High School to take part in a seven-part lecture series and to provide mentors, tutors, and laboratory tours for interested students. NIAMS also recently participated in the Blair High School Careers in Science Program, and the Institute provides support for the NCI Science Enrichment Program. Through our Stay-In-School Program, NIAMS provides opportunities for students to work for the Institute to support their education.

MINORITY HEALTH

Mr. Stokes. Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Shulman. NIAMS supports the career development and training of minority researchers through several programs, including Minority Access to Research Careers (MARC), Minority Biomedical Research Support (MBRS), and Minority Supplements. Through the Institute's active support of the Minority Supplements Program, we have almost doubled the number of individuals supported by NIAMS in the past three years. The Institute also supports programs at the high school level, such as the Adopt-A-School Program, in an effort to reach minority students and encourage them to pursue careers in biomedical research. Recently, representatives of NIAMS have participated in outreach programs directed at minorities, such as the VIII Hispanic Medical Congress, the MARC and MBRS Symposium, and the International College of Physicians and Surgeons: National Hispanic Youth Initiative in Health Policy Development.

The Institute's mandate encompasses several diseases, such as lupus, vitiligo, and spinal arthritis, that disproportionately affect or are of special concern to minority populations. The Institute supports research to study the causes of these diseases, and we have recently seen important advances in research on both lupus and spinal arthritis. To expand research on lupus, the Institute issued three Requests for Applications (RFAs) in FY 1993. As a result of these initiatives, the Institute is supporting 15 new basic research grants in lupus, including three population studies on the causes of the high prevalence of lupus among black women.

To expand programs in lupus outreach, the NIAMS Task Force on Lupus in High Risk Populations has updated its brochure, "What Black Women Should Know About Lupus," and has created a Community Program Kit with guidelines for developing community awareness programs. To improve outreach to Hispanics, the Institute has printed some public information materials in Spanish, including a bibliography of Spanish language materials for patients and physicians which was produced by our Information Clearinghouse. The Clearinghouse also has an information specialist available to answer inquiries in Spanish.

Mr. Stokes. What significant initiatives in minority health research and research training, and outreach are supported by your institute?

Dr. Shulman. The NIAMS supports initiatives in minority health research, research training, and outreach specifically in the areas of lupus, spinal arthritis and vitiligo. In lupus, a disease that disproportionately affects African American women, NIAMS supports both basic and clinical research with special emphasis on understanding why this disease is more prevalent in African Americans. The NIAMS Task Force on Lupus in High Risk Populations is expanding its efforts to inform women who are at risk of the disease by targeting its campaign in cities with high populations of minorities. Future plans of the Task Force include developing a professional education program for physicians and nurses in collaboration with the National Medical Association.

Similarly, NIAMS is pursuing research on vitiligo, a skin disease that is of concern to African Americans and spinal arthritis, a disease that has been shown to disproportionately affect Eskimos and Pima Indians.

Mr. Stokes. How does your Institute identify its priorities for investments in minority research and research training?

Dr. Shulman. NIAMS sets its priorities based on the scientific merit of research and training proposals. In doing so, the Institute tries to consider the needs of the many Americans who, at some point in their lives, will be affected by the diseases and disorders within our mandate. Since several of our diseases disproportionately affect minorities, we make every effort to support training programs and research supplements for minorities and minority institutions.

CLINICAL TRIALS

Mr. Stokes. How much is included in the FY 1995 budget request for clinical trials? How does this amount compare with the amount invested in clinical trials in FY 1994, and FY 1993? Would you please comment on the economic benefits, and the quality of life benefits of some of the major clinical trials supported by your Institute?

Dr. Shulman. The FY 1995 budget request includes $7.99 million for clinical trials. This amount reflects an increase of $373,000 or 4.9 percent over the FY 1994 estimate of $7.617 million, and an increase of $1.03 million or 14.8 percent over the FY 1993 actual of $6.96 million.

As a result of some of the Institute's clinical trials, we have seen benefits in terms of both economics and quality of life.

Some examples include a clinical trial conducted in the Institute's Intramural Research Program in which researchers found that treatment of patients suffering from lupus-induced kidney disease results in substantial savings and improved quality of life. The use of a combined drug regimen proved to sustain life-supporting kidney functions at a greater rate than single drug regimens, thereby reducing the need for costly dialysis or transplantation. This discovery has the potential to save the Nation up to $117 million each year in reduced treatment costs and lost earnings.

Other clinical trials supported by the Institute have shown that tick bites need not be treated prophylactically to prevent Lyme disease. We also have ongoing clinical trials regarding the use of exercise in the prevention of osteoporosis and the intake of calcium supplements by teen-age girls to build stronger bones. These types of clinical trials with a focus on proper treatment and prevention strategies have great potential to reduce the costs of disease and to improve quality of life.

Mr. Stokes. To what extent has the Institute increased the number of minorities participating in its clinical trials; what progress is being made?

Dr. Shulman. Since several of the diseases within our purview disproportionately affect minorities, NIAMS historically has had minority representation in our clinical trials. To increase recruitment in clinical studies, NIAMS has issued several supplemental grants to investigators to hire Spanish-speaking or African-American personnel to help with recruitment. The Institute has also worked to improve access to information for minority patients and physicians by printing public information materials in Spanish, and we support an Information Clearinghouse that has a Spanish-speaking information specialist to answer inquiries in Spanish. Outreach programs such as these have the potential to increase minority interest and participation in clinical trials.

Part of the Women's Health Initiative, a major NIH clinical trial, includes a series of studies on bone density being conducted by three centers in Pittsburgh, Alabama, and Arizona. Two of these centers are enrolling at least 60 percent minorities. The Chief of the NIAMS Bone Biology and Bone Diseases Branch is the project officer for the center in Arizona, in which the focus of recruitment is on Hispanics and Native Americans. The Alabama center is focusing on recruitment of African Americans.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes. I understand that a number of the institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Shulman. The NIAMS has actively supported the Minority Supplements Award Program since 1991. Since the program is relatively new, many of the recipients of the supplements have not had an opportunity to pursue grants through the traditional competitive process. NIAMS is currently developing a system by which we can track these individuals in order to evaluate the success of the program.

AFRICAN AMERICANS EMPLOYED AT GS-15 AND ABOVE

Mr. Stokes. How many GS-15 and above positions are there in your Institute? How many employees in your Institute are in GS-15 and above positions? In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze; if so, what was the response? If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Shulman. There are 23 GS-15 and above positions at NIAMS, and the Institute has 23 employees in GS-15 and above positions. Of these, one is an African American. This individual is a Health Scientist Administrator who is the Chief of the Grants Review Branch.

Presently, the Institute does not have any cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level. NIH has requested relief from the freeze, however, it has not been lifted as yet. If the freeze were lifted, it would help in our efforts to recruit minorities at all levels since it would enable us to recruit for positions from outside of the NIH and the PHS.

DISEASE PREVENTION

Mr. Stokes. With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your institute?

Dr. Shulman. Chronic diseases such as rheumatoid arthritis, osteoarthritis, and osteoporosis afflict millions of Americans causing tremendous human suffering and costing the United States billions of dollars in heath care and lost productivity. Scientific evidence is suggesting there are ways these diseases can be prevented and or delayed. For example, we know that osteoporosis is a preventable disease. New evidence has confirmed the importance of extra calcium and regular exercise in building stronger bones. Research has provided information on how estrogen replacement therapy is effective in reducing both post-menopausal bone loss and bone fractures. In June 1994, NIAMS will sponsor a consensus development conference to consider the influence of calcium intake on osteoporosis and to establish optimum levels of calcium intake for all age levels.

Other major prevention initiatives include the NIAMS Task Force on Lupus in High Risk Populations education campaign to inform those most at risk of lupus of the early signs and symptoms of the disease; research on preventing sports injuries in youth; and research in public and professional education for the prevention and control of skin cancers caused by exposure to ultraviolet radiation.

SUPPORT TO MINORITY INSTITUTIONS

Mr. Stokes. What is the present level of support provided to minority institutions by your Institute?

Dr. Shulman. In FY 1994, NIAMS estimates that funding for minority institutions will be $482,000.

Mr. Stokes. Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Institute's programs and activities.

Dr. Shulman. NIAMS supports programs such as MARC, MBRS, and Minority Supplements to provide training and funds to minority researchers and minority institutions. In addition, the Institute has recruited early admissions medical students from Howard University to perform research in NIAMS laboratories during our summer program. The Institute also has an Intramural Research Training Program in which selected MARC students participate in a ten-week research training program.

The Institute supports efforts to offer training to faculty members and students at historically black colleges and universities. Along with the Foundation for Advanced Education in the Sciences, Inc., the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Deafness and Other Communication Disorders (NIDCD), the NIAMS is sponsoring an upcoming program called Recombinant DNA and Special Topics in Biotechnology. This program offers biotechnology traineeships for faculty members of historically black colleges and universities and their designated student partners. The trainees will participate in a five-day lecture and laboratory course on biotechnology to provide insights and hands-on experience that the participants can share with other faculty and students at their institution.

UNDERREPRESENTED MINORITIES--RESEARCH AND TRAINING

Mr. Stokes. Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Shulman. To increase the participation of underrepresented minorities in biomedical research, NIAMS plans to increase funding for programs such as MARC, MBRS, and Minority Supplements. The Institute will also continue to support minority training programs and programs at the high school and college level that offer training opportunities for young students interested in careers in biomedical research.

HISPANIC HIRING AND PROMOTION

Mr. Serrano. Dr. Shulman, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions.

First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Shulman. NIAMS supports the recruitment and hiring of Hispanics into the field of biomedical research through several training programs. These programs encourage minorities to pursue research careers by providing funds and helping to improve access to career opportunities at NIH and elsewhere. In addition, the Institute attends conferences--such as the Hispanic Medical Congress, and the International College of Physicians and Surgeons: National Hispanic Youth Initiative in Health Policy Development--in an effort to increase access to and interest in research careers.

HISPANIC HEALTH

Mr. Serrano. Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Shulman. In FY 1993, the Institute spent $528,000 on programs specifically dedicated to the career development and training of Hispanic investigators. We also awarded $3.8 million in grants to 15 investigators who voluntarily identified themselves as Hispanic. In addition, the Institute funds researchers and research projects that focus on Hispanic health. For example, the Institute funds a Multipurpose Arthritis and Musculoskeletal Diseases Center at the University of California, Los Angeles, where one investigator is studying rheumatoid arthritis in Hispanic and white women. The goal is to improve the quality of life for homebound patients, and to compare how problems are managed within the two different cultures. In another research project on systemic lupus erythematosus (SLE) in women and minorities, the investigator has made an effort to specifically recruit Hispanics to participate in the study. The research will examine the socioeconomic, demographic, cultural, immunogenetic, and clinical factors underlying morbidity in minority groups. It will be the first systematic study of Hispanics with SLE in the U.S.

HISPANIC OUTREACH

Mr. Serrano. Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Shulman. NIAMS supports the career development and training of Hispanic investigators through several programs, including Minority Access to Research Careers (MARC), Minority Biomedical Research Support (MBRS), and Minority Supplements. In addition to providing support to Hispanic researchers through these programs, the NIAMS funded 15 investigators in FY 1993 who voluntarily identified themselves as Hispanic. The Institute also supports programs at the high school level, such as the Adopt-A-School Program, in an effort to reach minority students and encourage them to pursue careers in biomedical research. As a recent participant in the Blair High School Careers in Science Program, the Institute had a Hispanic researcher, who is a Ph.D. biologist in the NIAMS Arthritis and Rheumatism Branch, speak to students about the NIH High School Apprenticeship Program.

HISPANICS IN CLINICAL TRIALS

Mr. Serrano. Fourth, what is your institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Shulman. To increase recruitment of Hispanics in clinical studies, NIAMS has issued several supplemental grants to investigators to hire Spanish-speaking personnel to help with recruitment. In addition, the Institute has expanded its outreach efforts to Hispanics in several ways, including printing some of our public information materials in Spanish. We support an Information Clearinghouse that has developed a bibliography of Spanish language materials for patients and physicians and produced the information in both Spanish and English. The Clearinghouse also has an information specialist available to answer inquiries in Spanish. The Institute hopes that by improving access to information for patients and physicians, we can increase Hispanic interest and participation in clinical trials.

SUCCESS RATE FOR HISPANIC INVESTIGATORS

Mr. Serrano. Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Shulman. NIAMS does not have official figures on the number of qualified research applications submitted by Hispanic investigators since information about ethnic origin is not required on grant applications. Based on information received from voluntary questionnaires in which 40 percent of those asked did not respond, there does not appear to be any significant difference in the success rate of Hispanic investigators compared to the overall success rate for the Institute.

OSTEOPOROSIS

Mr. Bonilla. Could you update the subcommittee on the recent breakthrough on osteoporosis and what NIAMS hopes to accomplish in fiscal year 1995?

Dr. Shulman. There has been tremendous progress this year in osteoporosis research with the discovery of a gene that could facilitate early identification of individuals at risk for this disease. The gene codes for the vitamin D receptor and its metabolites. These metabolites influence many processes associated with bone, including bone turnover and the absorption and excretion of calcium. Osteoporosis usually results from a lack of sufficient bone mass and/or excessive rates of bone loss. Heredity has long been suspected of influencing bone density, but there has been little direct evidence for this until now. This new discovery calls for more research on the genetic regulation of bone turnover, the vitamin D receptor, and the actions of vitamin D and its metabolites on bone. NIAMS hopes to have the opportunity to fund additional research on this new finding in both FY 1994 and FY 1995. These investigations could lead to new targeted approaches to preventing osteoporosis.

NIAMS has also recently issued a Request For Applications for basic research. This initiative called "BONES" (Basic Research on Osteoporosis: New Experimental Strategies) invites applications on growth factors and other regulators of bone metabolism; the role of genetics in bone growth and remodeling; effects of androgens and estrogens on bone metabolism; and biomarkers. Awards will be made in the fall of 1994. NIAMS will also award a grant for establishment of a National Resource Center on Osteoporosis and Related Bone Diseases that will provide both patient and professional education materials on osteoporosis. Through these initiatives NIAMS hopes to stimulate the field of basic research on osteoporosis in order to enhance understanding of how to build strong bones throughout life. A further goal of the Institute is to improve and expand public education efforts.

In addition, NIAMS has invited several other Federal agencies to form a Federal Working Group on Bone Diseases. This group provides an excellent forum for all Federal agencies with programs on osteoporosis and related bone disorders to meet and discuss recent research accomplishments and initiatives and to plan for future collaborative activities. This working group has a full agenda for 1995.

Mr. Bonilla. What are NIAMS, NIA, and NCRR doing separately or jointly in the field of osteoporosis research?

Dr. Shulman. The NIAMS and the National Institute on Aging, as well as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute for Dental Research (NIDR), support very full and rich research programs on both basic and clinical research on osteoporosis and related bone diseases and disorders.

The National Center for Research Resources (NCRR) supports a number of General Clinical Research Centers (GCRCs) at which NIAMS and other institute-supported investigators conduct research on osteoporosis and related bone disorders. For example, a NIAMS-supported researcher conducting research on basic mechanisms of bone loss recently reported interim results from an ongoing clinical trial at The University of Texas Southwestern Medical Center at Dallas showing that treatment with fluoride and calcium supplements prevents new spinal fractures and helps rebuild spinal bones in patients with osteoporosis. The NCRR funds this clinical research center at the University of Texas Southwestern Medical Center.

The NIAMS, NIA, NIDDK, NIDR and the NCRR work collaboratively in a variety of ways to enhance research on osteoporosis. These institutes and the NCRR are all represented on the newly established Federal Working Group on Bone Diseases that was created under the leadership of NIAMS to provide a structure for sharing information and identifying areas of research collaboration and opportunity. In addition, these institutes and the NCRR will co-sponsor requests for applications to enable the NIH to support more research on osteoporosis. For example, the RFA inviting research applications on basic research on osteoporosis is co-sponsored by NIAMS, NIDDK and the NIA. In addition, the NIAMS and NIA are jointly sponsoring a program announcement on age-related changes in bone quality and the relationship of these changes to enhanced bone fragility and susceptibility to osteoporotic fractures.

FIBROMYALGIA

Mr. Bonilla. What does NIAMS plan to do in fiscal year 1995 regarding research for fibromyalgia syndrome (FMS)? Is it true that the older people get the more prevalent FMS becomes?

Dr. Shulman. The Request for Applications (RFA) for research on fibromyalgia that the Institute issued in October 1993 will be funded in September 1994, and we expect new research to be generated as a result. The response to the RFA was excellent, and we will be encouraging further research in this field.

Fibromyalgia is a disorder that can affect children and the elderly; recent research suggests that the peak frequency may occur around age 60.

Mr. Bonilla. What areas in the field of FMS research does your Institute place the highest priority on for funding purposes?

Dr. Shulman. The Institute plans to encourage all applications for high-quality research on fibromyalgia. Particularly promising areas are the interfaces between fibromyalgia and neuroendocrinology and between fibromyalgia and immunology. By better understanding the chemical and molecular pathways and mechanisms involved in the disease process, researchers can develop more specifically targeted therapeutic interventions.

Mr. Bonilla. The U.S. prevalence data on FMS reveals that two percent of the general population suffers with this chronic and potentially disabling condition. What do you see as NIAMS's role in furthering our understanding of the epidemiology and economic impact of this seemingly prevalent disorder?

Dr. Shulman. Current estimates of the prevalence of FMS are based on a population study in Wichita, Kansas. In that particular community, the prevalence was found to be approximately 2 percent. NIAMS has supported clinical epidemiologic research on the economic impact of fibromyalgia, as well as the disability associated with it, and we will continue to encourage similar investigations to better understand the magnitude of the problem.

NATIONAL INSTITUTE OF MENTAL HEALTH

SERVICES RESEARCH

Mr. Smith: Are you having any difficulty meeting the requirement in your reauthorization that you allocate 15 percent of your research budget to services research?

Dr. Cowdry: For FY 1994, the required increase for services research is $25 million of the total $30 million increase over the NIMH FY 1993 appropriation. Therefore, 83% of the total NIMH increase will be used to fund mental health services research.

In my opinion, this high priority placed by Congress and by the Institute on services research reflects a pressing need for more and better information about the effectiveness of treatments and about the organization and financing of mental health services to inform discussions of health care reform. Had this increase in services research come at any other time in the past decade, it would have been accommodated within the overall funding increase; but coming at a time of overall budgetary restraint, this increase has had a substantial impact on our ability to fund non-services research programs in FY 1993 and in FY 1994. NIMH anticipates future increases to be spread more equally once the set-aside percentage has been achieved.

RESEARCH TRAINING

Mr. Smith: You award the fourth highest number of research training grants in NIH -- more than twice the number of the Neurology Institute. Why do you place such a heavy emphasis on training compared to the other Institutes?

Dr. Cowdry: In recent years, there has been a tremendous growth in research in both basic neuroscience and the treatment of mental and behavioral disorders for patients of varying age, gender, and cultural and genetic backgrounds. This rapid growth has created a need for targeted efforts to train researchers in these fields, particularly the fields of child and adolescent mental disorders, services research, and prevention research, all of which are high priorities with Congressional mandates. The availability of capable scientists is an essential prerequisite to advancing research directed at understanding mental illness and behavioral disorders. NIMH also is concerned with increasing the numbers of women and minorities trained as researchers. In fact, only the NIGMS and the NIMH have special research training programs for promoting biomedical and behavioral research careers among minority individuals. At NIMH these include the Career Opportunities for Research Education (COR) program and the Minority Fellowship Program (MFP). However, maintaining a critical mass of talented, creative, highly motivated investigators is becoming increasingly difficult. In the decade from 1982-1992, the amount allotted for NIMH research training funds as a percent of the total research budget decreased by almost half--from 9 percent to 5 percent.

The FY 1995 President's Budget will fund the same number of FTTPs in the research training mechanism as in the FY 1994 appropriation, with an attendant funding increase for inflationary costs, not programmatic output.

SOCIAL WORK RESEARCH DEVELOPMENT CENTER

Mr. Smith: What is the social work research development center you are creating? Is it wise to broaden your outreach to additional professionals when your research grant success rate is already low?

Dr. Cowdry: The Senate in its report 103-143 stated, "The Committee instructs the NIMH to continue its efforts and activities directed toward developing social work research resources, including social work research development centers and targeting training initiatives for social work researchers, giving particular attention to the need to develop a cadre of minority researchers, including native Americans. The Committee expects the recommendations of the task force on social work research to be fully implemented and requests regular reports on the status of the implementation."

NIMH established the first social work research development center (R24) in FY 1993 at the George Warren Brown School of Social Work of Washington University in St. Louis, Missouri. Major objectives for the center are: 1) to strengthen the School's institutional capacity to conduct mental health services research, including enhancing individual faculty competence to conduct such research, and 2) to support substantively important projects by individual investigators. The Center's developmental and research activities focus on three key issues in mental health services delivery: access, integration, and effectiveness of care. This initiative also helps to accomplish another Congressional mandate to increase funding in services research where additional investigators are needed. A report on the Institute's implementation activities is being prepared for the Congress and it is currently in review.

Mr. Smith: Why are you terminating your Science Education Partnership Awards program?

Dr. Cowdry: The Institute has not terminated its Science Education Partnership Awards program. The program was begun under the auspices of the Alcohol, Drug Abuse, and Mental Health Administration. Since the Institute's return to the National Institutes of Health, the grants previously funded by NIMH have been transferred to the National Center for Research Resources where the NIH-wide science education program is contained.

HUMAN BRAIN PROJECT

Mr. Smith: What is the total cost of the Human Brain Project, and how many federal agencies are supporting it?

Dr. Cowdry: In FY 1993, NIMH spent about $1,233,731 on the Human Brain Project. The Institute expects that funding for FY 1994 will be approximately $3,080,000 and $4,250,000 in FY 1995. In

FY 1993, total Federal funding was approximately $2,619,000. NIMH is not able to project total Federal funding for FY 1994 or FY 1995, because new Federal components are continuing to join the effort and grant reviews and awards have not been completed. NIMH has, so far, recruited thirteen other Federal components to form the Federal Interagency Coordinating Committee on the Human Brain Project. These include: the National Institute on Drug Abuse; the National Institute on Alcoholism and Alcohol Abuse; the National Heart, Lung and Blood Institute; the National Institute on Aging; the National Institute of Dental Research; the National Library of Medicine; the National Institute on Child Health and Human Development; the National Institute on Deafness and Other Communication Disorders; the Fogarty International Center; the National Aeronautics and Space Administration; the Department of Energy; the Office of Naval Research; and the National Science Foundation.

CONFERENCES

Mr. Smith: According to a report the Department recently submitted to the Committee, your Institute spent $1.4 million on conferences in 1993. This total is more than the Cancer Institute, whose budget is about four times the size of NIMH. What is it about your mission that requires you to spend this amount on conferences?

Dr. Cowdry: In FY 1993, NIMH sponsored 29 conferences for $1,377,000. It should be noted, however, that $800,000, or 58% was used to support 12 conferences in three major, timely areas: the Decade of the Brain and Human Brain Project; psychopharmacology development; and multiple aspects of AIDS and its prevention. NIMH is leading 13 other agencies and institutes, as well as the supercomputer and information science communities in universities and Federal laboratories, in supporting the Human Brain Project. NIMH is playing a role complementary to that of the drug industry by addressing significant gaps in psychotherapeutic medications development--gaps that are critically important to people with specific mental illnesses. AIDS prevention breakthroughs require sharing information about effective programs that can be targeted at schools, and the development of intervention strategies that could be used in other community-based institutions, such as the workplace, prisons, and churches. Examples of the remaining conferences include: ethics and human subjects issues in mental health research with children and adolescents; women and minority issues in schizophrenia; a national symposium on eating disorders; a forum for mental health research in primary care settings; and mental health care under health care reform.

RESEARCH FUNDING

Mr. Smith: Identify the projected 1993-1995 funding for the following: schizophrenia, depression, bipolar disorder, panic disorder, youth suicide, Alzheimer's disease, and eating disorders.

Dr. Cowdry: NIMH estimated funding for the specified disorders for FY 1993-1995 follows:

Mental Disorder	FY 1993 Actual	FY 1994 Estimate	FY 1995 Pres. Budget
Schizophrenia..	$108,596,000	$114,487,000	$119,098,000
Depression.....	$125,324,000	$132,667,000	$138,276,000
Bipolar Dis....	$22,241,000	$23,371,000	$24,275,000
Panic Disorder.	$12,656,000	$13,402,000	$13,971,000
Youth Suicide..	$10,523,000	$11,287,000	$11,844,000
Alzheimer's....	$24,185,000	$25,443,000	$26,379,000
Eating Dis.....	$11,671,000	$12,322,000	$12,827,000

Mr. Smith: Identify the number, type, and subject areas of research centers supported in 1994.

Dr. Cowdry: In FY 1994, the NIMH anticipates funding the following research centers:

Subject Area	Continue	Renewal	New	Total
Schizophrenia	3	3		6
Mood/Anxiety/Personality	6	1		7
Aging	5	1		6
Child	1			1
Treatment	3			3
Human Brain Project	2			2
Behavioral,Cognition & Social Processes	2			2
Molecular and Cellular	6	3		9
Services Research	8	1	2	11
Prevention	4	1		5
Basic Prevention	2			2
AIDS	3	1	2	6
Total	45	11	4	60

Mr. Smith: Identify the mechanism used to finance the Institute director's compensation and benefits once he leaves NIMH, the duration of the arrangement, and the cost to the Federal government.

Dr. Cowdry: Dr. Frederick Goodwin, the former Director of NIMH, is being assigned to George Washington University under an Intergovernmental Personnel Act (IPA) detail for a two year period.

The cost to the Federal government for Dr. Goodwin's salary and benefits during this period will be approximately $134,000 per year.

SCHIZOPHRENIA

Mr. Stokes: I understand from your opening statement that research investigations have revealed that schizophrenia is the manifestation of an abnormality in brain development. Research further suggests that neurons having not completed their migrations during brain development, may not have made the appropriate connection with the rest of the brain. How much further along the path to prevention, intervention, improved treatment, and early detection does this knowledge place us?

Dr. Cowdry: The first and most important step in treating a disease is to understand its cause. While there has long been circumstantial evidence that neurodevelopmental abnormalities are associated with schizophrenia, only recently have we had direct evidence for this. A study of autopsied brain tissue from people with schizophrenia found evidence that certain nerve cells fail to complete their normal migration during brain development, which ordinarily takes place between the fourth and the sixth months of fetal development. In normal brains, these nerve cells were present in large numbers in the prefrontal cortex, while in the brains of individuals with schizophrenia, the nerve cells were concentrated in deeper layers of the cortex, showing evidence of failure to migrate to the surface of the cortex. Failure of these nerve cells to migrate properly may prevent them from making the critical connections between the prefrontal cortex and other parts of the brain.

Decreased activity of the prefrontal region has been seen in positron emission tomography (also known as PET) scans of patients with schizophrenia, compared with control subjects. We anticipate that progress in neuroimaging research may allow for the detection of specific brain changes in living subjects with schizophrenia early in the course of their illness. This could allow earlier diagnosis, and lead to new therapeutic interventions based on the brain abnormalities discovered.

Also, since it is clear that these neurodevelopmental abnormalities were present long before the major symptoms of schizophrenia developed (typically in early adulthood), it may be possible to detect individuals "at risk" for developing schizophrenia. By understanding the specific brain abnormalities responsible for symptoms of schizophrenia, it may become possible to target interventions specifically to compensate for these abnormalities. Discovery of underlying causes of schizophrenia symptoms could help to guide early treatment with antipsychotic or other medications, psychosocial/cognitive therapies, and interventions designed to prevent, delay the onset, or diminish the severity of schizophrenia.

Mr. Stokes: Have the knowledge, techniques and the technologies been developed to allow you to cross the bridge from development of schizophrenia to the prevention of it?

Dr. Cowdry: If the developmental mechanisms associated with schizophrenia are characterized in the near future, then we could identify individuals who may be at risk and/or specific conditions which may be contributory factors. Moreover, as our understanding of normal processes in the development of the brain increases, we will be in a better position to identify how specific aberrations affect circuits involved in cognition and behavior. This information coupled with our knowledge of the molecular events governing neuronal function will then expedite the development of new drugs or therapies for treating people afflicted with schizophrenia. However, it is difficult to predict the rate at which these advances will be made. Schizophrenia is a complex disorder which affects many of the fundamental workings of the brain which are in their own right major scientific research areas.

Advances in neuroimaging studies, neuroreceptor density measures, molecular genetic approaches, and other rapidly evolving technologies are being applied to the study of schizophrenia. Recent findings of substantial increases in a specific type of dopamine receptor (D4) will, if replicated, very likely lead to development of treatments to counteract this receptor imbalance. While clozapine, available in the US in the past several years, appears to block these D4 receptors and to diminish symptoms of schizophrenia, its troublesome side effects have limited its use. A new generation of safer medications with specific actions on the D4 receptor is currently being developed. Since research indicates that the longer an initial episode of schizophrenia remains untreated, the poorer the long-term outcome, early intervention with the proper medication could prevent substantial disability and deterioration.

Progress in molecular genetic approaches has been occurring at a breathtaking rate. NIMH is funding clinical research projects to discover the genes responsible for vulnerability to schizophrenia. By discovering specific genes which can lead to this disorder, there are great opportunities to better treat and eventually prevent the development of schizophrenia. For instance, when genes predisposing to schizophrenia are discovered, it should be possible to determine the normal functions of these genes. This would lead to early detection of individuals at risk, and the discovery of potential interactions between genetic and environmental factors. Locating the genes may also help to identify subtypes of schizophrenia, and permit determination of underlying biochemical abnormalities, leading to more effective new treatments. Since there are approximately 100,000 new cases of schizophrenia in the United States every year, progress would clearly have enormous public health implications.

MENTAL ILLNESS IN CHILDREN

Mr. Stokes: According to your opening statement, in general, mental illness affects one-fifth of the U.S. population. How extensive a problem is mental illness in children and adolescents?

Dr. Cowdry: We do not, as yet, have national data on which to base precise estimates of mental disorder among the nation's children and youth. Recent community-based epidemiologic studies found that up to 20 percent of children, aged 4-17, were affected by a mental disorder. Based on 1994 U.S. Census data, these results indicate that mental disorders may affect as many as 12 million U.S. children.

Severe mental disorder (as defined by the criteria of the Senate Committee on Appropriations) affected 3.2 percent of youth aged 9-17 studied in a recent multi-site methodologic community-based study.

Because of the lack of sound epidemiologic estimates concerning the prevalence and scope of mental disorders in children and adolescents, NIMH began a comprehensive program of research to address this and related questions. The Institute's latest efforts include a major, multi-site, child and adolescent study with three main goals: 1) to provide information on children's need for and use of services for mental health reasons, including barriers to mental health care; 2) to provide prevalence and incidence rates of specific mental disorders in child and adolescent populations; and 3) to expand our knowledge of the etiology and development of psychopathology. This project will address a critical public health need for solid, replicated, epidemiologic data on the prevalence of specific mental disorders among community populations of children and youth for mental health planning purposes and will help to attain objectives identified in Healthy People 2000.

Mr. Stokes: Have we made much progress in unraveling the cause, elaborate.

Dr. Cowdry: Significant progress has been made in the last decade in understanding several of the major mental illnesses in children and adolescents, most notably major depressive disorder, attention deficit hyperactivity disorder, conduct disorder, and obsessive compulsive disorder. The important role of genetic factors has been reasonably well established in a number of these conditions. Early childhood temperament and adverse environmental conditions have an impact on the severity and continuation of these problems. In several instances, major new treatments have been developed, and in other cases, new and promising treatments are now being tested. We feel that this area -- the study of childhood mental illness -- is one of continuing promise, and we expect we will see a continued expansion of exciting developments in this area over the next few years. Two recent examples of research findings include:

- Adolescent depression occurs at a crucial time, influencing future adjustment and substantially increasing the risk for future episodes of depression. An NIMH-funded study has recently found that 9.6 percent of a sample of 1700 entering high school students, coming from a wide cross section of ethnic and socioeconomic backgrounds, met the diagnostic criteria for depression. One in nine students had experienced two or more episodes, and relapse rates approached 20 percent.

- Several longitudinal studies funded by NIMH have found that even in high risk families--in which both parents have a mental disorder, where there is a strong family history of illness, and chaotic family life--some children remain free from the effects of mental disorders. Researchers call these children "resilient." As a group, these children were found to create a repertoire of coping skills early in their lives. Resilience may have both psychological and biological components and has important implications for prevention research.

BRAIN AND BEHAVIOR RELATIONSHIP

Mr. Stokes: What do we know about the brain and behavior that we did not know five years ago?

Dr. Cowdry: Brain and behavioral sciences have produced an explosion of new information in recent years. One specific area is a conceptual advancement in our understanding of plasticity in the brain. Plasticity refers to the ability of the nervous system to change. We have known for some time that plasticity is pivotal to the development of the brain, but we now realize that this process is a universal phenomenon throughout life. For example, learning and memory are forms of plasticity. This process occurs at all levels from molecules to cells to systems, eventually resulting in behavior. The core principle is that the brain is not "hard-wired," but is dynamically responsive to its environment. Factors which could cause plasticity in the brain can range anywhere from hormones to environmental toxins to social interactions. Clearly this concept has relevance in mental health because it predicts the existence of multiple strategies in developing treatments for mental disorders. Some examples of recent research results:

- "knock out genes" - specific genes can be deleted in animals to discover the relationship between the genetic code and behavior.

- "nitric oxide" and "carbon monoxide" - discovery of the use of volatile gases as messengers in the brain.

- "functional magnetic resonance imaging" - has been applied to learn about the areas of the brain involved with functions such as reading or categorizing.

- new discoveries of how the brain affects diverse functions such as the immune system and heart function.

- the ability of behavior (including social interactions) and learning to affect brain organization down to the level of the genes is only now being appreciated.

RESEARCH ADVANCES

Mr. Stokes: As the director of an institute of the NIH, the nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues -- while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and -- while medical and technological breakthroughs are affording Americans a longer life expectancy. Please elaborate.

Dr. Cowdry: Epidemiologic data show that there are no racial differences in the prevalence of most mental disorders. However, recent empirical studies, many of which have been carried out in NIMH-supported Minority Research Centers, are confirming cultural differences in the expression of symptoms, resulting in misdiagnoses and inappropriate treatment. NIMH is sponsoring studies of ethnically-defined populations as they respond to psychoactive drugs. The Institute also recently contributed to the development of guidelines on the effect of culture on the expression of mental disorders to be included in the new American Psychiatric Association's Diagnostic and Statistical Manual, DSM-IV.

A major factor affecting minority health (and the health of all Americans) is the health care delivery system. The Institute's research regarding the organization and financing of health care for mental illnesses and the effectiveness of the actual delivery of care in the community provides much needed data to guide discussions of health care reform. Part of this effort is specifically directed at services research issues in minority and rural populations.

Mr. Stokes: What are some of the most exciting and most promising basic research opportunities at your institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Cowdry: NIMH-supported research has produced many exciting findings in basic neuroscience and these advances have, in turn, opened new opportunities for progress against mental illnesses. Some of the most promising basic research opportunities include:

- Use the revolutionary breakthrough in functional magnetic resonance imaging (fMRI) technology that provides real-time maps of brain activity with incredible spatial accuracy to create detailed functional maps of brain activity.

- Take advantage of molecular biology tools, such as knock-out mutations and antisense RNA, to study the effects of specific neurotransmitters, receptors, second messenger systems, and ion channels on brain function, and use that information to create new animal models for studying the link between neuronal function and human behavior and mental illness.

- Foster the development of new techniques for recording and analyzing signals from multiple brain regions in the awake, behaving animal in order to begin understanding the role of neural networks in brain functions and the dynamic nature of neuronal signalling within and among brain regions.

- Expand research on functional neuroanatomy at all levels, from single neurons to neural systems, in order to better understand information processing in humans and the behaviors, both normal and abnormal, that can result.

- Strengthen research on the critical role of circadian rhythms, sleep, and dreaming in normal emotional and cognitive functioning, including interactions of brain sleep systems with neural, endocrine and immunological processes.
- Further explore the development of the brain both during and after birth, searching for key events whose timing is critical for proper brain development and determining how the environment, behavior, and cognition can modify events during brain development.
- Expand research on psychosocial and neurobiological development by linking behavioral and environmental forces with the anatomical, neurochemical, and hormonal factors that shape the development of critical functional capacities such as attention, self-regulation, learning, memory, emotion, and social behavior.
- Expand research on social-contextual processes in mental health and disorder, including interpersonal (e.g., family dynamics, parenting), societal (e.g., poverty, unemployment), and cultural factors (ethnic identity, minority status) that exacerbate or ameliorate vulnerability to mental disorder, and that influence service-seeking and the course and outcome of treatment.

In this, the Decade of the Brain, basic neuroscience and behavioral research stand at the brink of unraveling profound mysteries about the human brain and behavioral functioning. The explosion of information gleaned from basic neuroscience and behavioral science research in the recent past has presented us with remarkable opportunities to understand how the brain works: how individual neurons function and communicate with others; how memories are formed and learning occurs; how cognition and emotion develop; how genetic and environmental influences shape brain development and function; and how abnormalities in neuronal structure and function can lead to mental illnesses.

In addition, basic behavioral research carries this exploration further by providing the opportunity to understand how behavior unfolds within a person, and within the context of family, society and culture: how memories are formed and learning occurs; how cognition and emotion develop; how family and interpersonal processes affect psychological health; and how mental health is an interactive consequence of biology and social experience. The understanding of these processes is the essential unity of mind and body.

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your institute?

Dr. Cowdry: The availability of highly trained scientists is absolutely essential to future advances in understanding mental illnesses and behavioral disorders. Yet, maintaining a critical mass of talented, creative, highly motivated investigators is becoming increasingly difficult in a time of diminishing resources and expanding research needs. Nevertheless, NIMH is placing a high priority on attracting physicians and other skilled clinicians into research careers, and attracting basic scientists into careers studying topics germane to mental health issues. The Institute also is striving to broaden its population of researchers to ensure that women and racially and ethnically defined populations are appropriately represented. Most recently, the Institute has initiated a unique new program of dissertation research grants which provide support for graduate student training. The intent of these dissertation research grants is to assist in providing a positive and constructive research experience that will motivate a small but critical mass of candidates to make a commitment to research careers in one of three critical areas: child and adolescent developmental psychopathology, HIV/AIDS research, and mental health services research. The increased support for individuals who are training in developmental psychopathology and in mental health services research at this early juncture in their research careers is a natural consequence of recommendations in the NIMH National Plans, the "National Plan for Research on Child and Adolescent Mental Disorders" and "Caring for People with Severe Mental Disorders: A National Plan to Improve Services." The encouragement of developing investigators in HIV/AIDS research represents yet an additional effort to improve the quality of research and increase the number of researchers in this priority area.

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your institute, elaborate on the benefits to be achieved from further investments in this research.

Dr. Cowdry: The most exciting opportunities in clinical research address the biological foundations of mental illnesses and the development of more effective treatments. Further investments in this research will lead to a reduction in the suffering of millions of Americans with mental illnesses and a reduction in the $148 billion per year cost of these disorders to the Nation. For example, NIMH research has shown an important role for genetic factors in depressive illnesses, although the mode of inheritance is not yet known. There is recent evidence that some forms of depression demonstrate the phenomenon of anticipation in which the illness is more severe or occurs at an earlier age in successive generations. One NIMH study has identified 34 families with manic-depressive illness in which the age of onset decreased between 8.8 and 13.5 years from one generation to the next. Anticipation in other inherited disorders has been associated with a newly discovered genetic mechanism--an abnormal expansion of three-nucleotide-long sequences (so-called trinucleotide repeats) in DNA from generation to generation, until the sequences are large enough to disrupt gene function and cause disease. NIMH-supported investigators now are searching for trinucleotide repeat sequences in the genes of families with a history of affective disorder. To facilitate such genetic research, the NIMH Genetics Initiative is assembling volunteer families in which multiple family members have specific mental illnesses. DNA and diagnostic information will be provided to scientists anonymously for molecular genetics studies, including gene mapping.

As another example, research on panic disorder--which is marked by sudden, intense attacks of terror and irrational fear, an overwhelming sense of impending doom, and symptoms such as racing heartbeat, gasping for air, sweating, weakness, dizziness, and feelings of unreality--has provided breakthroughs in treatments. Individuals with panic disorder attempt suicide at a rate higher than that for depression and they also frequently, needlessly, seek treatment for cardiac problems; unnecessary angiograms performed because of panic disorder symptoms waste more than $32 million each year. NIMH-funded trials have demonstrated that the anticonvulsant drug valproate effectively reduces the frequency of panic attacks, and the antidepressant imipramine or anti-anxiety drug alprazolam reduces worry about having a panic attack in patients who have both panic disorder and mild-to-moderate depression. Drug therapy is not the only means for successfully treating panic disorder. NIMH-funded investigators have developed cognitive-behavioral therapies to help patients identify and change the misinterpretations of bodily sensations that can produce a panic attack. Over 80 percent of patients who undergo such therapy report that they no longer suffer from panic attacks, even two years after completing the therapy.

Studies of obsessive compulsive disorder (OCD) and related illnesses have grown to include Sydenham's chorea, a variant of rheumatic fever. Systematic evaluation of children with Sydenham's chorea by NIMH intramural scientists revealed that 75% had the abrupt onset of OC symptoms concomitant with the onset of their movement disorder. Antineuronal antibody measurements in these children, and a subgroup of children with primary OCD or Tourette's disorder, were positive during symptom exacerbations. Magnetic resonance imaging in acutely ill children revealed enlarged caudate nuclei which decreased to normal size following symptom remission. Acutely ill patients with either Sydenham's chorea or OCD have been treated with either plasma exchange, intravenous immunoglobulin, or prednisone. Pilot data have been encouraging as dramatic reductions in both motoric and psychiatric symptoms were observed. OCD is a common, debilitating mental illness, and medical models, such as that hypothesized in Sydenham's chorea, may provide insights into the etiology of this troublesome disorder. If a subgroup of patients can be identified who are at genetic, developmental, or neuroimmunologic risk, effective intervention and even prevention strategies may be devised.

Mr. Stokes: Please describe the measures your institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Cowdry: Fundamental to the advancement of research on minority populations is an increase in the number of minority investigators. Cognizant of this need, NIMH's research training outlays for such programs as the Career Opportunities in Research Education and Training grants (COR), Minority Institutions Research Development Program (MIRDP), and Minority Research Centers have grown rapidly in recent years. Also, since the 1970s, NIMH has supported highly successful Minority Fellowship Programs in several discrete disciplinary areas: psychiatry, psychology, nursing, social work, sociology, and, since 1988, neuroscience. One measure of success is seen in the neuroscience fellowship programs administered under the auspices of the American Psychological Association and the Society for Neuroscience. The programs now are the country's major single contributor to the advanced training of minorities in the basic neurosciences; in 1991 alone, they graduated 9 minority Ph.D.s in the neurosciences, more than doubling the 1989 output of the entire country. In 1991, a Minority High School Science Education Program was initiated. This program consists of supplemental awards to active COR grants aimed at encouraging minority high school students to select career disciplines related to research on mental and addictive disorders. These supplemental awards provide pre-college students with hands-on experience working on research projects with faculty and COR trainees over a 2-year period.

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your institute?

Dr. Cowdry: One significant initiative is a special program of research centers that focuses on all aspects of mental health related to minority groups. These include:

1. African American Mental Health Research Center, University of Michigan, Ann Arbor. These studies will contribute needed information on African American mental health by examining in detail the functions of social support, and the relationships between mental disorders such as depression and the seeking of both informal and professional help.

2. Hispanic Research Center, Fordham University, New York. This center's work focuses on epidemiologic-clinical studies in Hispanic mental health. There are five priority areas of research: emergence of problems, use of services, assessment, effective therapies and rehabilitation. Another goal is to increase the small pool of scholars trained in Hispanic mental health research.

3. National Research Center on Asian American Mental Health, University of California, Los Angeles, California. A landmark community epidemiologic study of mental disorders among Chinese Americans is estimating the prevalence of selected mental disorders and attempting to identify the factors associated with mental health problems in this population.

4. American Indian and Alaska Native Mental Health Research, University of Colorado Health Sciences Center, Denver, Colorado. Fewer than 70 doctoral-level investigators around the country are

actively engaged in mental health research among American Indians and Alaskan Natives. More than half of these are research associates of the Center, four are Native Americans.

5. Research Center on the Psychobiology of Ethnicity, Los Angeles County Harbor, UCLA California. Researchers are examining variations of dosage among minority patients. Several genetically influenced biological systems and environmental differences, such as diet, could be implicated in the differential effects of drugs. Other lines of research include how different groups understand routine psychiatric disorders.

Total Fiscal Year 1993 support for these programs was approximately $4,003,000.

Mr. Stokes: How does your institute identify its priorities for investments in minority research and research training?

Dr. Cowdry: The NIMH Office of the Associate Director for Special Populations, created in 1980 by the Public Health Service Act, has the responsibility to

(a) develop and coordinate prevention, treatment, research, and administrative policies and programs to assure increased emphasis on the mental health needs of women and minority populations;
(b) support programs and projects relating to the delivery of mental health services to women and minority populations, including demonstration programs and projects,
(c) develop a plan to increase the representation of women and minority populations in mental health service delivery and manpower programs;
(d) support programs of basic and applied social and behavioral research on the mental health problems of women and minority populations;
(e) study the effects of discrimination on institutions and individuals, including majority institutions and individuals;
(f) develop systems to assist women and minority populations in adapting to, and coping with, the effects of discrimination;
(g) support and develop research, demonstration, and training programs designed to eliminate institutional discrimination; and
(h) provide increased emphasis on the concerns of women and minority populations in training programs, service delivery programs, and research endeavors of the Institute.

The Office of Special Populations collaborates with the NIMH research divisions to make this mandate an Institute-wide effort.

Mr. Stokes. When your institute is developing new minority initiatives, does it seek advice from the Office of Research in Minority Health? To what extent is there a collaborative relationship between the two organizations, elaborate.

Dr. Cowdry: Most of the NIMH initiatives for minority populations were developed prior to our joining NIH. The Institute plans to collaborate in the future. In addition to the efforts of the Office of Special Populations described above, NIMH collaborates with the NIH Office of Research on Minority Health on funding research projects, which amounted to approximately $755,000 for seven projects in FY 1993.

CLINICAL TRIALS

Mr. Stokes: How much is included in the FY 1995 Budget Request for clinical trials?

Dr. Cowdry: In the FY 1995 Budget Request, $50,155,000 is included for clinical trials.

Mr. Stokes: How does this amount compare with the amount invested in clinical trials in FY 1994, and FY 1993?

Dr. Cowdry: In FY 1993, NIMH invested $45,757,000 in clinical trials, and in FY 1994 NIMH will spend an estimated $48,204,000 to fund clinical trials.

Mr. Stokes: Would you please comment on the economic benefits, and the quality of life benefits of some of the major clinical trials supported by your Institute?

Dr. Cowdry: The number of cost-effectiveness analyses based on economic data collected in clinical trials has been increasing during the last few years. NIMH supports a number of such studies which apply a variety of outcome measures. It is of note that these studies focus on quality of life issues as a specific outcome measure. These clinical studies with an economic component investigate the costs and benefits of alternative treatment methods for mental illness.

Some of the currently funded studies are:

- Cost-effectiveness of Six Treatments for Schizophrenia. This study is assessing the cost-effectiveness of six outpatient treatments for schizophrenia offered in the ongoing NIMH "Treatment Strategies in Schizophrenia" cooperative study. This study is a 5 site, 8 year collaborative clinical trial that compares 3 antipsychotic medication maintenance strategies in combination with 2 psychosocial family interventions in a 3x2 factorial design replicated at each site. The study will compare the cost-effectiveness of the six treatment combinations using a variety of effectiveness measures.

- Clozapine Treatment Outcome and Cost. The Connecticut Department of Mental Health has undertaken a study of costs and effectiveness of clozapine for severely ill patients being treated in the state's public mental health system. The methodology of this study was developed under another NIMH grant, "Services Trial Methods: Clozapine Cost-Effectiveness." This methodology enables state mental health agencies to compare the relative effectiveness and cost of clozapine versus usual services for treatment-resistant clients with schizophrenia.

- Cost-effectiveness of Dual Diagnosis Treatment. This research compares the cost-effectiveness of two approaches to treating people with co-occurring diagnoses of severe mental illness and substance abuse disorders. The research subjects have been randomly assigned to either Continuous Treatment Teams or traditional Community Support Programs. Cost-effectiveness of treatment alternatives is being analyzed from the perspectives of three groups: clients, families and treatment providers.

- Cost-effectiveness of Treatment for Depression. This project adds a cost-effectiveness analysis component to a clinical trial which is being conducted at the University of Pittsburgh to determine whether three types of treatments validated with depressed psychiatric patients are equally effective with depressed ambulatory primary care patients.

- Cost-effectiveness of PACT Programs In order to determine the appropriate place of the labor intensive PACT (Program for Assertive Community Treatment) programs in an array of community mental health services for severely and persistently mentally ill persons, policy makers need data on the cost-effectiveness of PACT programs as compared to other types of state of the art programs that are less intensive.

- Work Outcome in Depression, Anxiety, and Schizophrenia. These NIMH-funded researchers are analyzing the outcome data of 18 treatment investigations in these disorders to evaluate the effects of psychiatric treatments on the restoration of the capacity to work and more broadly to examine restoration of work function as an aspect of psychiatric recovery.

- Clinical Research Center for Study of Major Psychoses. This clinical trial is investigating the cost-effectiveness of clozapine administration to neuroleptic-resistant schizophrenic patients. The researchers are also studying the quality of life of these patients, which includes subjective and objective measures in the areas of living situations, family, social relations, leisure activities, work, finances, personal safety and health.

- NIMH Intramural Clinical Trial on Gaucher's disease. Previous achievements included making a transgenic mouse model of Gaucher disease by replacing the normal mouse gene with a defective gene. These mutant mice have symptoms and pathology analogous to what is observed in the severe human neonatal type. The NIMH intramural researchers are currently generating transgenic mice having milder forms of this human inherited metabolic disease, that affects approximately 10,000-20,000 Americans of primarily Eastern European Jewish ancestry. Treatment requires expensive enzyme infusions, costing $100,000 to $400,000 annually. In FY 1994, the IRP in collaboration with Enzon, Inc., has begun clinical trials of enzyme replacement for Gaucher disease.

- Multisite, multimodal treatment study of attention-deficit hyperactivity disorder in childhood.
  This study will employ and compare medication and behavioral treatments, alone and in combination. Only a multisite design can study enough affected children to determine which treatments and combinations of treatments, over a sufficient length of time, work best for different clinical presentations. Given the large number being treated in the community (1-2 percent of American children) and the very broad array of treatments now being used, this kind of scientific analysis is essential to improve and refine treatment strategies.

- AIDS Clinical Trials.
  NIMH has a major role to play in the planned AIDS vaccine trials, even though it does not have the mission to develop a prophylactic or treatment vaccine. The efficacy of the initial vaccines is unknown and there are important ethical issues associated with providing appropriate informed consent and behavioral interventions to persons at risk. NIMH has established a Workgroup on Behavioral Issues in Clinical Trials to develop research recommendations. This group is also identifying basic behavioral science issues that could be addressed within the clinical trials design. Other AIDS clinical trials include: (1) a multisite Phase II study of a peptide to treat the AIDS-related neurocognitive impairment, and (2) a key clinical trial initiative that is testing an AIDS prevention intervention across multiple populations in diverse geographic settings at 7 sites.

In summary, the NIMH portfolio reflects an increasing interest in moving beyond the measurement of symptom reduction as the sole measure of success for treatment trials to broader issues of treatment effectiveness--including quality of life and cost-effectiveness.

Mr. Stokes: To what extent has the Institute increased the number of minorities participating in its clinical trials?

Dr. Cowdry: NIMH has always been committed to including women and racial and ethnic minority groups and subpopulations in all of its research. All applicants who submit applications for research grants and cooperative agreements and proposals for contracts must follow the NIH policy of including women and racial and ethnic minorities in the study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. If all populations are not included or are inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided. The extramural and intramural communities have been educated on the requirements of the policy. Grant application forms require applicants to detail the composition of their study populations, and to report on actual accrual when they submit progress reports and apply for renewal. Similar requirements apply to intramural research and contracts.

In March, 1994, revised guidelines were published in the Federal Register. All NIH-supported biomedical and behavioral research involving human subjects must:

- For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished;
- not allow cost as an acceptable reason for excluding these groups; and,
- initiate programs and support for outreach efforts to recruit these groups into clinical studies.

Mr. Stokes: What progress is being made?

Dr. Cowdry: The revisions have not been in effect long enough to have had a measurable effect.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place?

Dr. Cowdry: The minority supplement awards program has been in place at NIMH since 1992. Since that time NIMH has expended approximately $7,000,000 in support of this program. In FY 1993, NIMH supported 36 new awards for a total of 87 (1 high school, 8 college, 36 pre-doctoral, 20 post-doctoral, 22 investigators) All minority groups are represented: Black 46, Hispanic 27, American Indian 2, Pacific Islander 8, and unspecified 4.

Mr. Stokes: Since its inception, how many minorities participating in the program have gone on the successfully compete for research project grants?

Dr. Cowdry: The average time of support for a supplement is 2 1/2 years. The program has not been in effect long enough for scientists to compete for research project grants.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of Historically Black Colleges and Universities in biomedical research?

Dr. Cowdry: Last year NIMH convened a meeting of the chairmen of the psychiatry departments in the four predominately Black medical schools. As a result of this meeting technical assistance teams, under the leadership of the Associate Director for Special Populations, were formed. All departments were visited. The purpose of these visits was to assist these departments in preparing planning grants, personal service contracts, purchasing of equipment, and other activities that will allow them to build and/or expand their infrastructure capacity. It must be noted that the Institute will allow maximum flexibility in assisting these institutions. It is our intent to allocate $300,000 - $500,000 over the next three years to support this activity. To date we have supplemented the RCMI grant at Drew for $25,000 for a series of workshops to begin in the Department of Psychiatry.

MINORITY EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Institute?

Dr. Cowdry: NIMH has a total of 81 GS-15 and above positions.

Mr. Stokes: How many employees in your Institute are in GS-15 and above positions?

Dr. Cowdry: NIMH currently has 77 employees in GS-15 and above positions.

Mr. Stokes: In your Institute, currently, how many African Americans are at the GS-15 and above level?

Dr. Cowdry: NIMH currently has three African-Americans on its staff at the GS-15 and above level.

Mr. Stokes: In what positions are they?

Dr. Cowdry: The positions they occupy are: Associate Director for Special Populations (SES); Deputy Associate Director for Special Populations (GS-15); and Supervisory Health Scientist Administrator (GS-15) in the Division of Extramural Activities.

Mr. Stokes: In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Cowdry: NIMH does not currently have any cases pending for exceptions to the freeze at the GS-15 and above level.

Mr. Stokes: Has the NIH requested relief from the freeze, if so, what was the response?

Dr. Cowdry: No relief has been sought for anyone at this grade level at NIMH.

Mr. Stokes: If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Cowdry: The NIMH employment ceiling will drop from 957 FTEs in FY 1994 to 929 FTEs in FY 1995. This offers the Institute little or no opportunity to hire new minority staff at any level. The current additional restriction on hiring or promoting individuals at the GS-14 and above level further restricts our ability to meet Affirmative Action goals.

PREVENTION RESEARCH

Mr. Stokes: With Health Care Reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Cowdry: Two recent reports have reviewed prevention research and recommended a prevention research agenda for the future. They include: 1) an NIMH Prevention Steering Committee Report entitled The Prevention of Mental Disorders: A National Research Agenda; and 2) a Congressionally-mandated Institute of Medicine Report entitled Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research.

These reports will serve as important guides for NIMH's future preventive intervention research activities. An Ad Hoc Committee of the National Advisory Mental Health Council has been formed to integrate the recommendations of the two reports and develop an Implementation Plan for Prevention Research. As part of the implementation process, NIMH is planning a National Prevention Conference to be held in November 1994.

NIMH currently supports a wide array of preventive intervention experiments including community based effectiveness trials which test the impact, in real world settings, of successful interventions previously tested in smaller scale, more highly controlled settings. It also supports Preventive Intervention Research Centers which form the basic infrastructure for expanding and enhancing the field of prevention research. Priority areas include the prevention of social and emotional problems among infants and young children at risk; the prevention of behavioral disorders and related problems in school aged children; the prevention of anxiety and depression in children and adults (including AIDS patients and their families); the promotion of mental health through the enhancement of protective factors; and the prevention of suicide and suicidality.

NEW RESEARCH AND BIOTECHNOLOGY

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Cowdry: As research unravels the roles of genes in mental disorders, it will be increasingly important to convert this knowledge into new therapies through research in biotechnology. NIMH already is funding projects that will contribute to methodology for gene therapy, gene transfer, and transgenic animals. For example, in the NIMH Intramural Program, researchers are working to produce transgenic animals that manufacture enzymes in their milk which can be isolated and used to treat Gaucher's disease, a rare, often fatal, inherited disease.

SUPPORT FOR MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Cowdry: During fiscal year 1993 the level of support for minority institutions was approximately $7,170,000.

Mr. Stokes: Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by Historically Black Colleges and Universities in the Institute's programs and activities.

Dr. Cowdry: The Institute supports a range of research and training opportunities. The Minority Fellowship Program for graduate students is designed to ensure that minority investigators assume a prominent position in research. The NIMH Career Opportunities for Research (COR) honors program provides support to college undergraduates. The Minority Institutions Research Development Program (MIRDP) aims to increase the capacity of predominantly minority institutions, and enhance the capability of their faculty, to conduct rigorous research. NIMH also has been strengthening its ties to Historically Black Colleges and Universities (HBCU) to encourage mental health and behavioral research. A special effort is being directed to schools of medicine as a base for mental health research in these populations. The Minority Dissertation Grant program has been conceived as a way to increase the number of Ph.D.s being awarded to students in these populations. The Institute hopes to fund approximately 10 of these awards a year in any area of relevant research. Among other accomplishments this year, NIMH funded the first regular research training grant at an HBCU for pre- and post-doctoral students.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research and research training.

Dr. Cowdry: NIMH supports five programs that are designed to increase the participation of minorities in behavioral and biomedical research and training. In addition to $4,003,000 in FY 1993 for Minority Research Centers, they are:

(1) Minority Institutions Research Development Program (MIRDP)
    Currently supporting faculty in nine institutions, four of which are HBCUs.
(2) Career Opportunities in Research Education and Training (COR)
    COR Faculty Fellowship Program
    In FY 1993, 99 students participated in the undergraduate honors program; 24 students in the high school program. Program data show that 75%-80% go on for advanced degrees, with half that number achieving Ph.D.
(3) Supplements for Underrepresented Minorities in Biomedical and Behavioral Research

In FY 1993, NIMH supported 36 new awards for a total of 87 (1 high school, 8 college, 36 pre-doctoral, 20 post-doctoral, 22 investigators) All minority groups are represented: Black 46, Hispanic 27, American Indian 2, Pacific Islander 8, and unspecified 4.

(4) Minority Fellowship Program

These grants support 134 trainees, about 80% have completed requirements for their doctorates.

The cost for these four programs in FY 1993 was about $9,775,000. The total cost for all five programs was approximately $13,778,000 in FY 1993.

HISPANICS AND NIH

Mr. Serrano: Dr. Cowdry, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Cowdry: NIMH is strongly committed to the basic principles behind the NIH's Equal Employment Opportunity program, which endorses the benefits of a diverse workforce. At the present time, we do not anticipate any hiring, insofar as our projected FTE ceiling for FY 1995 requires a reduction of 28 employees. However, you can be assured that any hiring that is done will include efforts to identify and recruit qualified Hispanic and other minority peoples. This would include position advertisements in minority oriented journals and contacts with various minority organizations.

NIMH is also aware of its responsibility to encourage Institute managers and supervisors to strongly consider Hispanic and other minority candidates for promotional opportunities. As an example of the Institute-wide commitment, NIMH appointed an Hispanic woman as its Personnel Officer in 1993.

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics).

Dr. Cowdry: During Fiscal Year 1993 NIMH expended approximately $6,500,000 on research specifically directed at Hispanic populations, which was 1% of the $583,142,000 budget. Approximately $59,000,000 more was spent on research related to Hispanic populations, or a total of 11%.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Cowdry: While we do not have an accurate estimate of the total number of Hispanic investigators supported by NIMH, we are funding three very important projects on Hispanic populations, for which the principal investigators are Hispanic.

(1) The Hispanic Research Center at Fordham University, Bronx, New York under the direction of Orlando Rodriguez, Ph.D. The goal of this Minority Mental Health Research Center is to conduct research on priority issues relevant to the mental health of the Hispanic population in the mainland United States and Puerto Rico. The research agenda is comprised of five integrated priority areas: 1) occurrence of mental health problems, 2) utilization of mental health facilities, 3) psychiatric assessment, 4) therapeutic modalities, and 5) post-treatment psychiatric rehabilitation. The Center also provides technical assistance, disseminates research findings, trains researchers, and addresses areas of national concern in the delivery of effective mental health services to Hispanics.

(2) A grant to Margarita Alegria, Ph.D., Principal Investigator, University of Puerto Rico, San Juan, Puerto Rico. "Mental health care utilization among Puerto Ricans." In one of the first comprehensive services research studies undertaken in Puerto Rico, the investigators have been surveying mental health services use by adult Puerto Ricans, particularly those in the lower socioeconomic strata. In-depth interviews were conducted in 1988 with 1,777 respondents drawn from a probabilistic islandwide sample. The current phase of the research involves two waves of follow-up interviews to examine changes in use of mental health services over time and identify factors associated with decisions to begin, stop, and continue using mental health care in a particular sector (public, private) or by a particular provider (generalist, specialist). Most important is that the design of the study allows findings from this research to be compared with similar studies conducted in the United States, such as the NIMH Epidemiology Catchment Area (ECA) study and the Hispanic HANES.

(3) A study on "Mental Health Services Utilization among Rural Mexican-Americans" is being conducted by William Vega, Ph.D., University of Southern California, Los Angeles. This study examines the mental health, substance abuse, and health services use of a representative sample of rural and urban adult Mexican Americans and Mexican nationals, aged 18 to 59, residing in Fresno, California. A multistage probability sample is being drawn from four strata: urban Fresno, rural Fresno County, small towns, and the migrant labor pool in that area. Information is being gathered on factors such as psychiatric morbidity, physical health, drug use, attitudes and beliefs, health insurance, socioeconomic status, immigration and occupational histories, and social network characteristics. In addition, data are being gathered on environmental and institutional factors, such as location, cost, staffing patterns, provider configuration, and clinician referral patterns. The investigator seeks to determine how culture, economics, and social networks interact with the financing and organization of medical care, in different areas, to influence use of services.

The Career opportunities in Research Education and Training (COR) has a High School component that provides hands-on research experience for promising junior and senior high school students who are interested in pursuing careers in science. Some other examples of outreach include the NIMH Minority Research Fellowship Program in Sociology and the Minority Research Fellowship Program in Social Work, which support predoctoral training for research careers in mental health. Both programs are responses to specific NIMH initiatives to increase the number of minority researchers. In the current fiscal year 10 of 27 social work fellows were Hispanic, and 7 of 29 sociology fellows were Hispanic. One undergraduate summer research training program at the University of California-San Francisco provides 10 weeks of intensive research involvement and preparation for graduate work to undergraduate students; in FY 1993 one-third of these trainees were Hispanic.

Mr. Serrano: Fourth, what is your institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Cowdry: NIMH has always been committed to including women and racial and ethnic minority groups and subpopulations in all of its research. All applicants who submit applications for research grants and cooperative agreements and proposals for contracts must follow the NIH policy by including women and racial and ethnic minorities in the study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. If all populations are not included or are inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided. The extramural and intramural communities have been educated on the requirements of the policy. Grant application forms require applicants to detail the composition of their study populations, and to report on actual accrual when they submit progress reports and apply for renewal. Similar requirements apply to intramural research and contracts.

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- not allow cost as an acceptable reason for excluding these groups; and,
- initiate programs and support for outreach efforts to recruit these groups into clinical studies.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Cowdry: NIMH does not have reliable data on the racial or ethnic designation of applicants because it is supplied on a voluntary basis to NIH. NIMH does not have access to this information.

EATING DISORDERS

Mr. Porter: In December, the McKnight Foundation announced $4.6 million in grants related to eating disorders. What was the Institute's role in this program?

Dr. Cowdry: The McKnight Foundation (a private charitable foundation) recently announced this program to address the escalating problem of eating disorders among adolescents and youth. The McKnight Foundation has provided more than two-thirds of all private foundation support for research on eating disorders over the past ten years. This new Program was designed to complement current research and provide a strong foundation for future research funding by the Foundation as well as NIMH.

The new program is multi-faceted. It includes the development and pilot testing of methodologies for large-scale research expected to be supported subsequently by NIMH, a data center, and an information and training component.

The McKnight Foundation's $4,600,000 commitment is allocated as follows:

- $3,6000,000 will support research aimed at improving diagnosis and treatment.
- $500,000 will support the establishment of a new data center.
- $500,000 will fund projects to improve prevention and recognition of eating disorders and referral for treatment among professional people working with at-risk young people.

The McKnight program was designed with the advice of experts from major medical institutions, NIMH, and clinics providing community-based treatment to those who suffer from these disorders. In addition to providing guidance about the scope of eating disorder problems and gaps in knowledge, NIMH staff participation helped to ensure that the McKnight Program complements and extends NIMH's eating disorders support.

Mr. Porter: What is the status of NIMH-funded research on eating disorders, how much was dedicated to eating disorders research in 1993 and 1994, and how much is contained in the 1995 budget request?

Dr. Cowdry: NIMH funded $11,671,000 in research on eating disorders in FY 1993 and estimates that it will fund $12,322,000 in FY 1994. The President's Budget Request includes $12,827,000 in funding for research in this area. NIMH is supporting treatment trials of cognitive/behavioral therapy, medication, and the combination of these therapies. Comorbidity of eating disorders with other mental disorders is a severe problem that is under consideration for a program announcement. NIMH is cooperating with the American Psychiatric Association in developing treatment guidelines. In addition, to raise awareness of symptoms, NIMH is coordinating with the SAMHSA Center for Mental Health Services, which has a mandate to disseminate public information on eating disorders, and with the Office of Women's Research at the Department of Health and Human Services.

Examples of recent accomplishments in the field of eating disorder research include:

- A recent NIMH-funded study of women with anorexia found that nearly half the anorexic and mixed subjects no longer met full diagnostic criteria for at least 8 consecutive weeks during the first year after completing psychotherapy for the disorder. It is well-established that individuals with bulimia recover more often than do those with anorexia or both disorders. Total recovery at one year -- no symptoms of the disorder -- was seen in 56% of bulimia patients, compared to 18% of women with both anorexia and bulimia and 10% for women with anorexia alone. It is not known how many of these "recovered" patients stay symptom-free beyond one year, suggesting that a long-term monitoring effort is needed to get a better understanding of the prognosis for these disorders.

- Several NIMH-supported studies have shown that antidepressant drugs which affect serotonin systems in the brain reduce binging and purging behavior as well as the depression and anxiety associated with bulimia. Researchers are focusing on cholecystokinin (CCK), a neuroactive peptide that is associated with satiety. Measurements of CCK in the cerebrospinal fluid of women diagnosed with bulimia and in healthy volunteers showed that bulimia sufferers had significantly lower levels of this peptide. Neurobiological studies have shown that CCK interacts with serotonergic systems in the central nervous system, and that CCK's ability to suppress food intake depends on intact function of central serotonin pathways. These findings suggest that the connection between decreased CCK concentrations, serotonin systems, bulimia, and anxiety is one well worth pursuing.

- Recent studies have suggested that both obsessive compulsive disorder (OCD) and anorexia nervosa improve during treatment with serotonergic antidepressants. Hyperactivity is also a common symptom of both disorders. NIMH intramural researchers are studying food-restriction induced hyperactivity in rats as a new model for OCD and anorexia nervosa. Preliminary results show that fluoxetine (Prozac), an antiobsessional serotonin-reuptake blocker, decreases excessive running, increases food intake, and slows down the weight loss process of laboratory rats. Should this animal model of obsessional illness be confirmed, NIMH researchers could use it as a guide in developing psychopharmacological interventions for persons with these disorders.

SERVICES RESEARCH

Mr. Porter: Current law requires the NIMH to expend at least 15% of its budget on services research. What effect does this have on the budget overall, and what is your opinion of the mandate?

Dr. Cowdry: For FY 1994, the required increase for services research is $25 million of the total $30 million increase over the NIMH FY 1993 appropriation. Therefore, 83% of the total NIMH increase will be used to fund mental health services research.

In my opinion, this high priority placed by Congress and by the Institute on services research reflects a pressing need for more and better information about the effectiveness of treatments and about the organization and financing of mental health services to inform discussions of health care reform. Had this increase in services research come at any other time in the past decade, it would have been accommodated within the overall funding increase; coming at a time of overall budgetary restraint, this increase has had a substantial impact on our ability to fund non-services research programs in FY 1993 and in FY 1994. NIMH anticipates future increases to be spread more equally once the set-aside percentage has been achieved.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

INTRAMURAL RESEARCH PROGRAM

Mr. Smith: Is the principal focus of your intramural program the genetics of hearing impairment? Given the staffing constraints that all the NIH institutes face, could this research be conducted extramurally?

Dr. Snow: One of the two principal themes of our intramural program is the molecular genetics of nonsyndromic hereditary hearing impairment. The NIDCD intramural research program chose this area of emphasis because the state of the science lends itself to rapid progress; there is inadequate activity in the extramural community; and the potential outcome will benefit large numbers of people. In addition, the NIDCD intramural research program has high-quality investigators that were ready to meet these program needs. However, the future quality of this research focus depends on the ability of our intramural program scientists to provide guidance and stimulate research experiences in new investigators, as well as to invigorate established scientists through collaborative efforts.

Important progress has already been made as a result of our intramural research program. Our scientists have taken a major leadership role by establishing two important genomic collaborations, the Waardenburg Syndrome Consortium and the Usher Syndrome Consortium, to accelerate progress on the identification and characterization of genes responsible for these two syndromes.

The NIDCD is well aware of a need to accomplish a balance between the intramural and extramural components of its mission and has, through an external Board of Scientific Counselors, the National Deafness and Other Communication Disorders Advisory Board, and the National Deafness and Other Communication Disorders Advisory Council, received expert advice about the appropriateness of the projects selected for intramural investigation.

AVERAGE COST

Mr. Smith: Why does your average cost of a new grant in 1995 increase by more than the biomedical research deflator (6.0% versus 4.1%)?

Dr. Snow: The NIDCD is anticipating awarding 83 new research project grants in FY 1995. The estimated average cost of these new research project grants is $172,550, which is a 4.1% increase over FY 1994.

RESEARCH TRAINING

Mr. Smith: In the early days of your Institute, it was emphasized that there were extremely few ear-nose-throat specialists trained to conduct research. How many researchers are now practicing in this area? Do you feel you devote an adequate share of your budget to research training?

Dr. Snow: Only about 5-10% of the principal investigators of NIDCD research grants are M.D.s. Strikingly, the number of ear, nose and throat specialists (otolaryngologists) who are principal investigators has remained virtually constant between 1976 and 1993, ranging between 16 and 23. One of the primary concerns of the Institute's Research Training Program is enhancing the cadre of physicians substantively involved in research across the Institute's mission areas. This topic will be a focused area of discussion during a program planning workshop on research training to be conducted by the Institute on May 25-26, 1994. The NIDCD expended 3.2% of its budget on training compared to the average of 2.9% for training for the NIH. The NIDCD believes that the share of its budget devoted to research training is appropriate to the growing research needs in its mission areas.

SMALL BUSINESS INNOVATION RESEARCH

Mr. Smith: Do you extensively use the small business research mechanism- SBIR--in your work on assistive hearing devices?

Dr. Snow: The SBIR program has and continues to support many projects on assistive hearing devices. For example, scientists participating in the NIDCD SBIR program have made technologic improvements in vibrotactile devices, which convert sound energy to vibrations which are delivered to the skin. A person whose hearing impairment is so severe that hearing aids are of little or no benefit can receive important speech information through their sense of touch, allowing for improved communication. For those whose hearing impairment presents a threat to safety, work is well underway toward completing the development of a novel signal processing system to identify and describe important household, workplace, and environmental sounds to hearing-impaired individuals. If this technology can be successfully developed, it could be used for a wide variety of medical, industrial, and consumer applications for which automatic identification or characterization of sound would be useful. An assistive listening device that incorporates many modern technologies (including infrared and FM) into one device is complete. This device, released on the market in 1993, allows a hearing-impaired user to purchase a single device with multiple modalities instead of purchasing individual units for each purpose, thus providing cost savings as well as greater convenience for the user. In addition, the microphone designed for use in this device has proven to be of great benefit in noisy situations and may improve other listening devices, including hearing aids and cochlear implants.

Mr. Smith: What share of your research project grant pool is comprised of SBIRs?

Dr. Snow: Approximately 2.15 percent of the funds available for research project grants will support SBIRs in FY 1995.

RESEARCH FUNDING

Mr. Smith: Provide estimated 1993-1995 spending on the following: hearing aid development, otitis media vaccine, Meniere disease, stuttering, noise-induced hearing loss, tinnitus, and Williams syndrome.

Dr. Snow: In hearing aid research and development, the NIDCD spent $6,074,000 in FY 1993; we estimate we will spend $6,342,000 in FY 1994; and $6,575,000 in FY 1995. The NIDCD currently supports over 30 grants related to hearing aid research and development.

The NIDCD and the Department of Veteran Affairs (DVA) have implemented a plan that allows for the immediate initiation of new hearing aid research, as well as for sustained efforts in this important endeavor. This collaboration promises to address the needs of those individuals that rely on hearing aids for communication.

In otitis media vaccine research, the NIDCD spent $153,000 in FY 1993; we estimate we will spend $300,000 in FY 1994; and $500,000 in FY 1995. The importance of nontypable Haemophilus infuenzae (NTHi) as a cause for otitis media and the continued emergence of antibiotic resistant NTHi strains indicate the need for the development of a vaccine to prevent otitis media caused by NTHi. The Division of Intramural Research (DIR), NIDCD, has initiated a research program to develop a vaccine against NTHi-caused otitis media. Intramural scientists are attempting to make a lipopolysaccharide-derived oligosaccharide-protein conjugate vaccine which would be important for the prevention of otitis media in infants and young children.

In Meniere's disease research, the NIDCD spent $563,000 in FY 1993; we estimate we will spend $585,000 in FY 1994; and $608,000 in FY 1995. Researchers are currently actively searching for the antibodies that are induced by and react with inner-ear antigens in individuals diagnosed with Meniere's disease and the relationship between patterns of antibody reactivity and clinical presentation of the disease. If specific inner-ear antigens can be related to Meniere's disease, a much needed clinical diagnostic test for this debilitating disorder can be developed.

In stuttering research, the NIDCD spent $929,000 in FY 1993; an estimated $972,000 will be available in FY 1994; and $1,009,000 in FY 1995. The Division of Intramural Research is currently conducting research aimed at improved diagnosis and treatment of stuttering.

New brain imaging techniques (positron emission tomography) have been used to study brain activity during stuttering in comparison with brain activity in fluent speakers. The NIDCD has completed controlled trials of new methods for controlling stuttering in chronically affected adults not benefitted by speech-language therapy.

In noise-induced hearing loss research, the NIDCD spent $5,417,000 in FY 1993; an estimated $5,638,000 will be available in FY 1994; and $5,847,000 in FY 1995. Scientists have known that the susceptibility of hearing loss as a result of exposure to noise varies from individual to individual. These variations cannot be attributed entirely to age, gender, ethnic origin, or pre-existing hearing loss. Early research results suggest that the ear may be acclimatized to withstand the effects of loud noise with little residual permanent effect on hearing.

Tinnitus is a symptom of diseases and disorders of the auditory system. The NIDCD spent $88,075,000 in FY 1993; an estimated $92,654,000 will be available in FY 1994; and $95,992,000 in FY 1995 for hearing research. Tinnitus is a very common problem; 15 to 20 million Americans have tinnitus. It varies in severity as far as how distracting it is. The understanding of tinnitus will come from research related to normal hearing and the dysfunction related to multiple hearing disorders.

In Williams syndrome (WMS) research, the NIDCD spent $226,000 in FY 1993; an estimated $239,000 will be available in FY 1994; and $247,000 in FY 1995. WMS is a genetic disorder characterized by unusual facial features, cardiac and dental anomalies, hypercalcemia, and mental retardation. Recent studies of children with WMS challenge the belief that the level of language ability of children tends to be equal to their level of function in other cognitive areas. Despite the presence of severe general cognitive deficits, linguistic abilities are selectively preserved in WMS. Although young WMS children and children with Down syndrome are remarkably similar in their language delays, they exhibit dramatically different skills once they reach adolescence. By uncovering differences between the two groups in the early stages of prespeech and language development, insights will be gained in what causes the contrasting abilities in language and cognition that are evident in adolescence.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject matter of research centers supported in 1994.

Dr. Snow: The NIDCD supports six Comprehensive Centers and ten Specialized Centers.

The six Comprehensive Centers include multidisciplinary research projects, research training, continuing professional education and information dissemination to the public. NIDCD supports comprehensive centers for Research and Training in Hearing and Balance, Hearing Loss in Children, Voice and Speech Communication, Otoneurologic and Vestibular Clinical and Basic Research, Neurogenic Communication Disorders, and Otolith/Canal Control Mechanisms in Posture and Movement.

Among the Specialized Centers, there are two in the areas of hearing and balance. They are investigating Rehabilitation Strategies for Hearing-Impaired Persons and Cochlear Implantation. In the senses of smell and taste, NIDCD supports three specialized centers in Chemosensory Clinical Research. Voice, speech, and language research is advanced through specialized centers in Aphasia, Dynamics of Speech Articulation, and Studies of Papillomas from the Upper Respiratory Tract. NIDCD supports a specialized center on Origins of Communication Disorders and a specialized Clinical Research Center for Communicative Disorders in Children.

SENSORY CELL REGENERATION

Mr. Porter: Dr. Snow, sensory cell regeneration may someday permit physicians to restore hearing. What is the status of your research in this area?

Dr. Snow: The ability of the inner-ear tissue to repair itself under experimental conditions after drug-induced toxicity and noise trauma is well established. Hair cell production can be reactivated by the inner-ear supporting cells of the adult bird under these conditions, and the regenerated cells establish functional neural connections. Recently, regeneration of the inner-ear vestibular hair cells of adult mammals (guinea pigs and humans) has been demonstrated in culture. This dramatic finding raises the possibility of the recovery of inner ear mediated balance function in higher mammals. Research efforts are proceeding with great intensity to determine the growth factors that trigger the mammalian inner-ear supporting cells to proliferate in response to injury. If such triggering factors can be identified for both the auditory and vestibular inner-ear hair cells, approaches to deliver these chemicals to the inner-ear can be devised, holding the promise of restoring hearing and balance function.

ENVIRONMENTAL IMPACT ON HEARING IMPAIRMENT

Mr. Stokes: Today, there is a ongoing dialogue about the impact of the environment on health. What can you tell about the environmental impact on hearing impairments?

Dr. Snow: Noise, various drugs, and certain chemotherapeutic and chemical agents are ototoxic and thus, induce hearing loss. Noise-induced hearing loss affects some 10 million Americans, and more than 20 million people in the United States are exposed to dangerous levels of noise. Aminoglycoside antibiotics, clinically important and commonly used drugs, can produce hearing loss in individuals receiving therapy and in the fetus if the mother receives therapy during pregnancy. Cisplatin and carboplatin, chemotherapeutic agents used in the treatment of cancer, can result in hearing deficits in a large number of individuals. Organic solvents, used in the chemical and manufacturing industries, such as toluene have also demonstrated ototoxicity in both animals and humans. NIDCD scientists are working to understand the mechanisms underlying ototoxicity in order to diagnose, treat and ultimately prevent these disorders.

The NIDCD joined other NIH Institutes and federal agencies and physician groups in a recent planning meeting for a conference to be held in November 1994 on air pollution impact on body organs sponsored by Physicians for the Environment and supported by NIEHS. NIDCD had held its own conference resulting in a teleconference and public education packet, "Changing the Future" now available.

SENSORY CELL REGENERATION

Mr. Stokes: How close has research in sensory cell regeneration placed us in being able to restore or even prolong good hearing?

Dr. Snow: It has been known for a few years that hair cell regeneration can occur under experimental conditions following injury to the inner ear of the adult bird and that the regenerated cells establish functional neural connections. The ultrastructural properties of the hair-cell progenitors, the supporting cells, and the nature of the molecular signals responsible for initiating regeneration are being actively investigated by NIDCD-supported scientists.

Recently, hair cell regeneration has been demonstrated in culture in the vestibular hair cells of the mammalian inner ear. If the chemical factors triggering regeneration can be identified, regeneration of auditory hair cells may be possible in higher mammals. If this sensory cell regeneration can be shown to maintain or restore hearing and balance function, the NIDCD will support research into ways of delivering the regeneration-initiating substances to progenitor cells.

RESEARCH TRAINING OPPORTUNITIES

Mr. Stokes: What is the Institute doing to attract and increase the number of students, especially minority students, pursuing research careers in human communication?

Dr. Snow: The NIDCD has enhanced the research training of minority individuals by promoting the NIH-wide program for Research Supplements for Underrepresented Minorities since its inception in 1989. Furthermore, the NIDCD has been among the Institutes joining the National Institute of General Medical Sciences in the support of predoctoral research fellowships for minority students enrolled in doctoral programs in the biomedical and behavioral sciences.

The NIDCD sponsored a Working Group on Research and Research Training Needs of Minority Persons and Minority Health Issues in April 1992. The recommendations of that expert panel continue to guide us in developing effective strategies for attracting individuals into communication sciences. For example, as a result of the Working Group we have also established the NIDCD Partnership Program, a comprehensive minority research and training demonstration program between the NIDCD and four academic centers with large enrollments of minority persons currently underrepresented in biomedical and behavioral research. The program supports curriculum improvement and student/scientist/administrator exchange with the NIDCD. Participating institutions are: The Morehouse School of Medicine/Atlanta University Complex, the University of Alaska System, the University of Puerto Rico, and Gallaudet University. During the NIDCD-sponsored Working Group on Research Training Needs of Graduate Programs in Communication Sciences and Disorders, held in January 1994, panelist emphasized the need for attracting new scientists to human communication research, especially minority investigators. When the Working Group report is formally presented, we will have another resource of information and guidance for our future training plans.

The NIDCD also encourages participation of minority students in scientific meetings and research forums by providing travel fellowships for minority students. The Institute anticipates that exposure to basic and clinical research developments will attract minority students to pursue careers in communication sciences. The NIDCD will support 10 minority students attending the first hearing aid conference, "Advancing Human Communication" in 1995.

The NIDCD is also co-sponsoring an innovative training course for minority students, the Faculty-Student Partnership Traineeship in Biotechnology in FY 1994. Courses emphasizing recombinant DNA technology will be supported.

On May 25- 26, 1994, the Institute will conduct a program planning workshop, titled, "Training Researchers for the Next Century in the Communication Sciences." The primary purpose of this workshop is to evaluate mechanisms previously not utilized by the NIDCD that would serve to enhance the Institute's research training mission. Among the topic areas to be addressed during this event will be approaches to increase racial and ethnic diversity in NIDCD-supported training programs.

AQUIRED HEARING IMPAIRMENT

Mr. Stokes: To what extent does childhood hearing infections result in and cause hearing impairment? How can this acquired hearing impairment be prevented?

Dr. Snow: Otitis media the leading cause of acquired hearing impairment in childhood and costs the nation billions of dollars each year for health care. Despite the availability of antibiotics against those bacterial species involved, there is frequent recurrence of the disease and persistence of the sequelae. Antibiotic resistant bacteria continue to emerge.

Otitis media is caused by several microorganisms, the most important of which are the pneumococcus and nontypable Haemophilus influenzae. We need vaccines against both of these microorganisms to prevent the vast majority of otitis media. Vaccines effective in infants against the pneumococcus are entering phase I and II clinical trials. The Intramural Research Program is working to identify a suitable candidate antigen for a vaccine against nontypable Haemophilus influenzae.

NUTRITION AND DISEASE PREVENTION

Mr. Stokes: Today, we are learning more and more about the direct relationship between nutrition and disease prevention. How extensive is the research in this area at your Institute? Is that research geared toward a specific disease or for the advancement of disease knowledge in general, explain?

Dr. Snow: Research opportunities and needs regarding the relationship between nutrition and disease prevention relate to each of the NIDCD's mission areas: hearing, balance, smell, taste, voice, speech, and language. Nutrition research has been a strong component of the NIDCD smell and taste program. Studies of the relationship between taste preferences and nutrient intake are important in the development of strategies to modify the dietary intake of individuals with various medical conditions, such as metabolic disorders and hypertension. For example, research shows that dietary manipulations have a profound effect on the development of salt preferences. Animal model deprivation studies show that dietary salt restriction during early development results in a subsequent decrease in responsiveness to salt. These studies suggest that components of breast milk, such as sodium, may have critical effects on later food preferences.

The NIDCD is actually participating in the preparation of a new trans-NIH initiative on Bionutrition which will be issued in FY 1995.

INVESTMENTS IN MOLECULAR BIOLOGY RESEARCH

Mr. Stokes: Can you highlight for us what advances could stem from increased investments in molecular biology, as is related to the diseases and disorders under the purview of your Institute?

Dr. Snow: The vast majority of all hearing impairment is genetically determined. Advances in molecular biology are providing information on the chromosomal location of the genes responsible for different forms of hereditary hearing impairment. These techniques also permit us to determine if these genes are present in members of families at risk for the development of deafness. Evidence from NIDCD-funded research now indicates that some forms of hereditary hearing impairment (e.g., Usher syndrome, and Waardenburg syndrome) may be dependent on multiple genes; the disposition to develop deafness may be dependent on one gene, while the actual manifestation of deafness may be dependent on the concomitant presence of other genes. These data explain why some members of families who carry the Usher or Waardenburg genetic defect may possess the gene and yet have normal hearing. Disorders of human communication such as childhood language impairment, dyslexia and stuttering could benefit from increased research utilizing molecular biological approaches. Although there has long been evidence suggesting a genetic component for these disorders, the detailed mapping of the gene loci involved has not yet been achieved.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your Institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly.

Dr. Snow: Many scientists in both the intramural and extramural programs of the NIDCD have made important progress in the identification of the genes responsible for many of the hereditary diseases that fall within the mission of the NIDCD. Identifying the genes responsible for a given disease is a critical first step in the initiation of gene therapy research. Major diseases and disorders that are poised to reap the benefits of advances in gene therapy include many forms of syndromic and nonsyndromic hearing impairment such as Usher syndrome and Waardenburg syndrome. With continued progress in gene identification, there is reasonable hope that many forms of hearing impairment may soon be understood and that therapeutic somatic intervention to prevent the development of these diseases is in the foreseeable future.

Mr. Stokes: How much is included in the FY 1995 budget request for gene therapy?

Dr. Snow: An estimated $8.0 million will be available to support the molecular studies required to pursue gene therapy research.

Mr. Stokes: How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Snow: In FY 1993, the NIDCD obligated an estimated $7.5 million and, in FY 1994, an estimated $7.8 million will be obligated for the molecular studies related directly to gene therapy.

MINORITY HEALTH ISSUES

Mr. Stokes: With regard to diseases and disorders that affect minorities, what are the most significant areas of research that are supported and conducted by your Institute?

Dr. Snow: Otitis media (ear infections) and noise-induced hearing loss are two problems for which some minority groups may have a greater incidence and which could be related to a lack of readily available health care or health care information. The NIDCD is expanding its research for vaccines against otitis media, including a collaborative effort with the National Institute of Child Health and Human Development and the Center for Biologics Evaluation and Research of the Food and Drug Administration to identify suitable vaccine (antigen) candidates and for developing conjugate vaccine(s). In the area of noise-induced hearing loss, scientists have recently uncovered a mechanical basis for the temporary partial hearing loss that accompanies exposure to loud sounds. This has important practical implications because exposure to noise continues to be the major cause of acquired hearing loss in adult populations.

Mr. Stokes: As the Director of an Institute of the NIH the nations principal federally-supported biomedical research investment, how would you respond to the statement, the Minority health crisis continues--while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and while medical and technological breakthroughs are affording americans a longer life expectancy. Please elaborate.

Dr. Snow: The NIDCD is concerned about minority health issues and is using the recommendations of a working group held in 1992 to aid in its ongoing identification of diseases and disorders of human communication that disproportionately affect minorities. Currently, the Institute's Epidemiology Branch is working on redesigning the Health Interview Survey to yield better information about minorities, and the NIDCD's National Human Temporal Bone Hearing and Balance Pathology Resource Registry includes minorities as subgroups. The Institute has an ongoing program announcement on the Identification and Treatment of Childhood Language Impairment in Multicultural Populations and plans to issue a request for proposals on the Development of a Theoretically Based, Methodologically Sound and Culturally Unbiased Language Test Instrument in Fiscal Year 1995.

RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising basic research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research?

Dr. Snow: Examples of exciting NIDCD basic research studies include: 1) Genetic Hearing Impairment: Research is contributing to the elucidation of Usher syndrome which is characterized by profound deafness and retinitis pigmentosa. These basic studies hold promise of gene therapy in the future for certain forms of deafness. 2) Ototoxicity: Life threatening bacterial infections must frequently be treated with antibiotics that themselves are ototoxic and threaten to damage hearing and balance function. Basic studies are contributing to an understanding of this potential complication of medical treatment and will help eradicate it. 3) Hair Cell Regeneration: Many forms of hearing impairment are the result of destruction of the hair cells in the inner ear. Until recently it has been assumed that once this destruction occurs the damage is irreversible and the hearing deficit must remain. However, it has now been shown in a variety of animals that regeneration of these damaged cells can take place to a greater or lesser extent under certain circumstances. Attention is now focusing on the ways in which this form of regeneration can be encouraged, in the hopes of providing therapy for hearing impairment for which none exists at the present time.

In the auditory and vestibular systems, glutamate receptors are involved in neurotransmission at the sensory cell and at most other excitatory synaptic populations. In addition to their direct roles in neurotransmission, glutamate receptors are also known to be involved in a range of other events including neuronal development, neurotoxicity, and neuronal plasticity in response to injury. One of our intramural research laboratories is studying these basic events in the production of glutamate receptors to determine how a disruption at any point may affect auditory function.

Understanding the mechanisms which regulate a complex neuronal protein such as a receptor will provide fundamental information on how a neuron functions and how it develops and maintains synaptic connections with other neurons. Such knowledge may lead to the development of novel therpeutic drugs which modulate receptor expression.

We are applying a newly developed technique, differential display, to attempt to identify cochlear genes whose expression is affected by experimental manipulation of the auditory system. Differential display is promising to our analysis of the cochlea because it not only allows for displaying different labeling patterns between two or more samples that contain very little tissue, but the cDNAs exhibiting these differences can be cloned and the genes identified.

Identifying known genes whose expressions in the cochlea change under various experimental conditions would offer important insight into understanding normal and abnormal cochlear events. Furthermore, these studies may lead to the identification of genes involved in human genetic disorders which affect hearing.

Squamous cell papillomatosis of the larynx in children and adults and carcinomas involving the vocal tract in adults destroy the airway and organs involved in speech and are the most common neoplasms affecting human communication. Moreover, squamous cell neoplasms of the head and neck lead to 18,000 deaths annually in the U.S. New approaches to therapy are needed to preserve speech and improve survival. Basic and clinical research in the Tumor Biology Section of Head and Neck Surgery Branch of NIDCD is directed towards development of new biologic, immunologic and gene therapies for these neoplasms. Retinoids are naturally occurring and synthetic compounds that hold promise in reinstituting the regulation of attachment receptors that help abnormal cells invade and destroy normal tissue. Interleukin 12 is an immune cytokine hormone which offers promise in reprogramming the body's helper T cell immune response to fight these neoplasms more effecively. Immune cytokines which can be transferred to the tumor cells of the individual by gene therapy are being tested to find out if they can help immunize individuals against the neoplasms.

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure conditioned advances in the research areas under the purview of your Institute?

Dr. Snow: The NIDCD recognized the need to ensure an adequate pipeline of highly trained researchers to meet the challenges ahead in the scientific mission areas of the Institute. To meet these needs, the Institute has made a concerted effort to foster training at the predoctoral level. This effort has resulted in a 2.6-fold increase in the number of predoctoral positions filled on NIDCD-supported training grants during a three-year period. One of the ten new training grants added to the Institute's portfolio over the last three years includes a unique dual-track doctoral program providing rigorous training in the speech and hearing sciences and in medicine, engineering, psychology. All available trainee positions in this program have been filled since its inception by highly qualified students exhibiting a high level of commitment to the communication sciences. Other new training programs funded by the Institute over the last three years address the underserved areas of the language sciences and the clinical chemosensory sciences. In addition, the five currently funded National Multipurpose Research and Training Centers (RTCs) provide the Institute with an important infrastructure for supplying the needed pipeline. The training components of the RTCs span all educational levels from high school students to independent investigators.

RESEARCH OPPORTUNITIES

Mr. Stokes: What are some of the most exciting and most promising clinical research opportunities at your Institute, elaborate on the benefits to be achieved from further investments in this research?

Dr. Snow: Otitis media is one of the most common infectious diseases of childhood. Institute-supported researchers are now using a variety of molecular biological approaches including the development of vaccines to improve our understanding of this problem and thus available modes of prevention and treatment.

Many individuals suffer from genetically based inability to detect specific odors. This is a problem increasingly prevalent with advancing age. It has now been shown that repeated exposure to a specific odor induces the ability to detect the odorant although none existed before. This finding has enormous potential for clinical benefit.

Scientists using advanced microcomputer and video technology are constructing an American Sign Language (ASL) video dictionary with which a user may type in an English word and be shown on screen the appropriate signs. The three dimensional nature of this system allows for actual representation of signs in space. The dictionary will have wide-spread use by deaf and hearing ASL-users in this country.

NIDCD scientists have recently discovered that brain activation patterns in stuttering adults differ from normal not only during stuttered speech but also during oral movements and humming. Because brain functioning abnormalities can be seen in people who stutter even when they are not speaking, this suggests that the neurogenic abnormalities underlie stuttering. Further studies are aimed at determining if brain organization differences can be found early during speech development of children who stutter. The long term goal is to identify the factors underlying these brain functioning abnormalities and to prevent the development of stuttering.

Spasmodic dysphonia is a disorder that results in voice abnormalities in midlife and disrupts speech. Neurogenic abnormalities are being studied in individuals with spasmodic dysphonia which might explain what causes this disorder to develop. Several hypotheses are now being tested in human and animal models. If confirmed, these studies could lead to an early intervention which could prevent these symptoms from developing following their initial onset.

RESEARCH TRAINING/OUTREACH ACTIVITIES

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Snow: The National Institute on Deafness and Other Communication Disorders (NIDCD) Partnership Program is a comprehensive minority research and training demonstration program between NIDCD and four academic centers with large enrollments of minority persons currently underrepresented in biomedical and behavioral research. Each minority academic center in the program has developed objectives relative to the intent of the program and their specific needs. These objectives include: establishment of symposia, career fairs and curriculum revisions in the areas of hearing, balance, smell, taste, voice, speech and language; expansion of research and training efforts involving human communication; and recruitment of high school, undergraduate, graduate and medical students to careers in human communication. In addition, the NIDCD sponsored a Working Group on Research and Research Training Needs of Minority Persons and Minority Health Issues in April 1992. The recommendations of that expert panel continue to guide us in developing effective strategies for research initiatives and outreach efforts. During the NIDCD-sponsored Working Group on Research Training Needs of Graduate Programs in Communication Sciences and Disorders, held in January 1994, panelists spoke of attracting new scientists to human communication research, including those of minority groups. When the Working Group report is formally presented, we will have another resource of information and guidance for our future training plans. In the area of outreach, our public education vehicle, "I Love What I Hear," is intended to educate third through sixth graders about noise-induced hearing loss and, at the same time, teach them about the fascinating biology of hearing. The program is being distributed to all 50 states and to urban, rural, and suburban school districts. The National Center for Neurogenic Communication Disorders at the University of Arizona in Tucson, one of our National Multipurpose Research Training Centers, has a special interest in outreach to American Indian and Hispanic populations. Information is disseminated in a number of ways, from video training programs and photonovellas for the Hispanic community to radio and billboard advertisements and photomurals. Also, the NIDCD is working with the National Medical Association (NMA) in its efforts to offer information to African American audiences on the risk factors for diseases that are preventable. Through a community coalition health pilot program, the NMA and the NIDCD will tailor relevant messages and themes to billboards (replacing cigarette and alcohol billboards), busboards, and PSAs in fourteen inner cities. The NIDCD is undertaking a spanish language version of this campaign to appear in publications nationally.

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your Institute?

Dr. Snow: The NIDCD Partnership Program looks to the cooperative efforts of our Institute, the Office of Research on Minority Health, and the participating institutions of Morehouse School of Medicine/Atlanta University Complex, the University of Alaska System, the University of Puerto Rico (as well as Gallaudet University) in the support of curriculum improvement and student/scientist/administrator exchange, with the goal of maximizing the opportunities for underrepresented minorities to participate in fundamental and clinical research in human communication. The Institute is collaborating with the National Medical Association (NMA) to offer information to African American audiences on the risk factors for diseases that are preventable. Working closely with the NMA to tailor messages and themes to billboards, busboards, and PSAs in fourteen cities, the NIDCD will emphasize the importance of early identification of hearing impairment in young children, the importance of hearing conservation, and the problem of noise-induced hearing loss. The NIDCD has also Spanish versions of many of its publications, including program area fact sheets and general brochures.

MINORITY RESEARCH AND RESEARCH TRAINING

Mr. Stokes: How does your Institute identify its priorities for investments in minority research and research training?

Dr. Snow: The NIDCD has enhanced the research training of minority individuals by promoting the NIH-wide program for Research Supplements for Underrepresented Minorities since its inception and programming supplemental grants using this mechanism. Furthermore, the NIDCD has been among the Institutes joining the National Institute of General Medical Sciences in the support of predoctoral research fellowships for minority students enrolled in doctoral programs in the biomedical and behavioral sciences. On May 25-26, 1994, the Institute will conduct a program planning workshop, titled, "Training Researchers for the Next Century in the Communication Sciences." The primary purpose of this workshop is to evaluate mechanisms that would serve to enhance the Institute's research training mission. Among the topic areas to be addressed during this event will be approaches to increase the racial and ethnic diversity in NIDCD-supported training programs. The recommendations emerging from the coming workshop and the continued advice the NIDCD receives from the scientific community enable the Institute to formulate its priorities in stimulating and programming research on minority health issues and research training for minority persons.

COLLABORATION WITH THE OFFICE OF RESEARCH ON MINORITY HEALTH

Mr. Stokes: When your Institute is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health?

Dr. Snow: Yes. The Partnership Program was developed in consultation with the Office of Research on Minority Health, and the office has been involved in the implementation process.

Mr. Stokes: To what extent is there a collaborate relationship between the two organizations? Elaborate.

Dr. Snow: Through an Interagency Agreement between the NIDCD and the Office of Research on Minority Health, the recently established NIDCD Partnership Program will provide support for improvement of curriculum and current research activities, and for the exchange of students, scientists, and administrators in order to maximize the opportunities for underrepresented minorities to participate in fundamental and clinical research in human communication.

CLINICAL TRIALS

Mr. Stokes: How much is included in the FY 1995 budget request for clinical trials?

Dr. Snow: In FY 1995, an estimated $5.9 million will be available to support clinical trials.

Mr. Stokes: How does this amount compare with the amount invested in clinical trials in FY 1994, and FY 1993?

Dr. Snow: The NIDCD obligated $5.4 million in FY 1993 for clinical trials, and approximately $5.7 million will be available for FY 1994.

Mr. Stokes: Would you please comment on the economic benefits, and the quality of life benefits of some of the major clinical trials supported by your Institute?

Dr. Snow: The NIDCD currently support clinical trials across all of the program areas of the Institute. This includes research on cochlear implants, otitis media, chronic vestibular dysfunction, and the treatment of aphasia, spasmodic dysphonia, and laryngeal papillomas. Clinical trials, in contrast to other phases of investigation, hold potential benefit not only for these patients but for the long-term improvement of quality of life for others who have or will have similar conditions. Economically, this would translate into dollars saved from ineffective treatments, lost wages and reduced job success. We are hopeful that NIDCD clinical trials will ensure both economic and personal benefits across all areas of human communication.

Mr. Stokes: To what extent has the Institute increased the number of minorities participating in clinical trials, what progress is being made?

Dr. Snow: All applicants for NIH grants and cooperative agreements that involve human subjects are required to include racial/ethnic minority subjects and both genders in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, and conditions under study. This requirement is evaluated by the review group for every application. Once a grant is funded, each Health Scientist Administrator is responsible for assuring that the grant-holder is successful in recruiting and retaining minority subjects. Specific to the mission of the NIDCD, otitis media (ear infection) is one area in which some minority groups may have a greater incidence. The NIDCD is expanding its research of vaccines against otitis media with an emphasis on minorities. In addition, the NIDCD currently funds two National Multipurpose Research and Training Centers (RTCs) with clinical trial components. These RTCs have resulted in increased involvement of minority subjects; they have placed special emphasis on attracting African-American, Native American and Hispanic-American subjects.

MINORITY RESEARCH SUPPLEMENTS

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since the inception, how many have gone on to successfully compete for research project grants?

Dr. Snow: The NIDCD has been actively participating in the Minority Supplement program since its inception in 1989. This Institute has been one of the leaders at the NIH in percent of investigators with these supplements. NIDCD has taken an active role in generating interest in this program. For example, on several occasions, each Principal Investigator supported by the Institute received information regarding this program and encouragement to apply. A mechanism is now in place to alert every newly-awarded grantee about the availability of the program. In addition, contact has been made with each of the 117 Historically Black Colleges and Universities alerting them to this program and encouraging the research offices of those institutions to serve as a liaison between their students or faculty and NIDCD supported researchers around the country. It is premature to expect recipients of these supplements to have obtained independent grant support, given the limited amount of time since the program began and the level of student (undergraduate/graduate) typically supported by NIDCD under this program. However, there is every expectation that such support will be obtained by many of these individuals.

INCREASED PARTICIPATION OF HBCUs

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of Historically Black Colleges and Universities in biomedical research?

Dr. Snow: One of the participating academic centers in the NIDCD Partnership Program is The Morehouse School of Medicine/Atlanta University Complex. Through this program, both students and faculty will have the chance to learn from NIDCD scientific and administrative mentors in NIDCD facilities. Training support mechanisms will include: Intramural Research Training Award (IRTA) (pre- and postdoctoral); Intergovernmental Personnel Act (IPA); NIDCD Extramural Visiting Scientist-Administrator Program; Staff Fellowship Program; Clinical Associate Program; Clinical Elective Program; and the NIH Summer Program. Funds will also be provided for travel, supplies and partial stipends or salary support.

MINORITY EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Institute? How many employees in your Institute are in GS-15 and above positions? In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your Institute, how many African Americans are among the cases pending for exception to the freeze on appointments and promotion to the GS-15 and above level? Has the NIH requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Snow: There are 15 positions at the GS-15 and above level in the NIDCD. There are eight SES positions and 7 GS-15 positions. In the NIDCD there are twelve employees in the GS-15 and above positions. At the GS-15 level, there are four nonminority females and three nonminority males. At the SES level, there are four nonminority males and one Asian male. There are no African Americans in positions at the GS-15 and above level. At the present time, this Institute is under an NIH-imposed freeze as well as the PHS freeze. We do not have any exceptions pending at the GS-15 and above level. The NIH requested relief from the Public Health Service hiring freeze imposed in December 1993 because NIH had successfully managed its FTE ceiling. The request is under consideration by the PHS. The NIDCD will try to improve the workforce profile in the categories of minorities and persons with disabilities in positions that have been targeted under the NIH/NIDCD Affirmative Action Plan.

PREVENTION RESEARCH

Mr. Stokes: With health care reform on the horizon, there is increased interest in and a value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at your Institute?

Dr. Snow: The NIDCD is supporting a number of research projects related to the prevention of diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. For example, a multicenter collaborative study is underway to ascertain the most robust, reliable, and cost-effective means of assessing hearing in neonates. The importance of early intervention to minimize or prevent the disabling effects of hearing impairment makes early diagnosis desirable. Other prevention research studies are investigating the early identification of language impairments in preschool children, with the goal being the reduction and prevention of long-term communication and academic impairments.

Noise-induced hearing loss, which is often preventable, affects millions of Americans. The NIDCD has produced and disseminated widely a videotape and teacher's guide, "I Love What I Hear!," for use with third through sixth graders designed both as a prevention message and as an introduction to the biology of hearing.

BIOTECHNOLOGY RESEARCH

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your Institute?

Dr. Snow: Many notable advances in molecular and cellular biology have recently occurred, such as the demonstration of regeneration of sensory cells in the vestibular, hearing, smell and taste systems, the identification and cloning of many of the genes that cause diseases and disorders that fall within the purview of NIDCD, and the characterization of the membrane properties of the sensory and neuronal elements of the inner ear. Each of these advances in biomedical science has come about because of enabling techniques and technologies. Advances in biotechnology are also necessary for the optimization of the use of prosthetic devices. For example, new technology related to implantable materials should enable the placement of auditory prostheses at any of the many nuclei of the auditory nervous system, thus allowing the clinician to bypass the nonfunctional parts of the hearing system. Other such advances likewise stand to restore sensory or motor function to the millions of hearing-, balance-, smell-, taste-, voice-, speech-, and language-impaired people in the United States who previously had no such hope.

MINORITY RESEARCH

Mr. Stokes: What is the present level of support provided for minority institutions by your institute?

Dr. Snow: In FY 1993, the NIDCD provided approximately $5.0 million for minority research.

INCREASED PARTICIPATION OF HBCUs

Mr. Stokes: Minority Institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding and they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by Historically Black Colleges and Universities in the Institute's programs and activities?

Dr. Snow: The NIDCD views its Partnership Program as a way to develop the human infrastructure of minority institutions. By providing a unique research and research training opportunity to institutions such as the Morehouse School of Medicine/Atlanta University Complex, we not only hope to increase the number of minorities conducting investigations into human communication but also enhance the research skills of those already in the field. The program objectives will enable NIDCD staff to: understand better the complexities of problems in the mission areas of the NIDCD being addressed by minority individuals and institutions; develop strategies jointly with the academic centers for establishing new and innovative programs and improving present research and training activities; recommend activities for students, faculty and administrators for career development; recruit and retain individuals from underrepresented groups to careers in the disciplines served by the NIDCD and provide opportunities at the Institute's headquarters in Bethesda, Maryland; and promote NIDCD extramural and intramural staff career development. In January 1994, the NIDCD cosponsored a seminar on Recombinant DNA and Special Topics in Biotechnology for Students and Faculty of Historically Black Colleges and Universities.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research, and research training?

Dr. Snow: The NIDCD provides approximately $5.0 million to support the National Research Services Awards, which provide research opportunities for pre and postdoctoral individuals.

The NIDCD anticipates providing approximately $1 million in FY 1995 to support Minority Supplements to Research Project Grants. The Institute will continue to support the Minority Biomedical Research Support program and the Partnership Program in FY 1995.

EMPLOYMENT OF HISPANIC INDIVIDUALS

Mr. Serrano: First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute.

Dr. Snow: The NIDCD has developed a Federal Equal Opportunity Recruitment Program (FEORP) Plan to implement new NIH FEORP guidelines. The plan calls for the development of generic recruitment plans that can be used by NIDCD selecting official when recruiting for FEORP vacancies. As part of the FEORP activity, the NIDCD has received a list of Hispanic organizations and will be contacting these sources to determine their interest in receiving vacancy listings. The list also identifies several Hispanic magazines and journals to be reviewed to determine their usefulness in the NIDCD's recruiting efforts.

The NIDCD recently established a Partnership Program which is a comprehensive minority research and training demonstration program between the Institute and four academic centers with large enrollments of minority persons currently underrepresented in biomedical and behavioral research. The University of Puerto Rico is one of the academic centers. Through a memorandum of understanding between the NIDCD and the NIH Office of Research on Minority Health, the program will provide support for improvement of curriculum and current research activities, and for the exchange of students, scientists, and administrators in order to maximize the opportunities for underrepresented minorities to participate in fundamental and clinical research in human communication. The University of Puerto Rico has developed objectives relative to the intent of the program and its specific needs. These objectives include: establishment of symposia, career fairs and curriculum revisions in the areas of hearing, balance, smell, taste, voice speech and language; expansion of research and training efforts involving human communication sciences; and recruitment of high school, undergraduate, graduate and medical students to careers in human communication. The first two students will be arriving from Puerto Rico the last week of May 1994.

HISPANIC HEALTH ISSUES

Mr. Serrano: Second, What percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed to Hispanics)?

Dr. Snow: In FY 1995, approximately 1 percent of the NIDCD budget will directly support Hispanic Health issues.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create pre-university pipeline?

Dr. Snow: The NIDCD recently established a Partnership Program which is a comprehensive minority research and training demonstration program between the Institute and four academic centers with large enrollments of minority persons currently underrepresented in biomedical and behavioral research. The University of Puerto Rico is one of the academic centers. Through a memorandum of understanding between the NIDCD and the NIH Office of Research on Minority Health, the program will provide support for improvement of curriculum and current research activities, and for the exchange of students, scientists, and administrators in order to maximize the opportunities for underrepresented minorities to participate in fundamental and clinical research in human communication. The University of Puerto Rico has developed objectives relative to the intent of the program and its specific needs. These objectives include: establishment of symposia, career fairs and curriculum revisions in the areas of hearing, balance, smell, taste, voice speech and language; expansion of research and training efforts involving human communication sciences; and recruitment of high school, undergraduate, graduate and medical students to careers in human communication. The first two students will be arriving from Puerto Rico the last week of May 1994.

The National Institute on Deafness and Other Communication Disorders (NIDCD) funds five National Multipurpose Research and Training Centers (NMRTCs) which has resulted in increased involvement of minority students in both short-term and predoctoral training. These multidisciplinary centers have placed special emphasis on attracting Hispanic, as well as African-American, and Native American, students. A grant to the National Center on Neurogenic Communication Disorders at the University of Arizona (Tucson) entitled "Speech Breathing Kinematics Across the Human Life Span" focuses on neurogenic speech and language disorders. Research training includes predoctoral and postdoctoral education. In addition, continuing education and information dissemination programs focus on the Hispanic and Native American populations in particular.

CLINICAL TRIALS

Mr. Serrano: Fourth, what is your institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Snow: All applicants for NIH grants and cooperative agreements that involve human subjects are required to include racial/ethnic minority subjects and both genders in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, and conditions under study. This requirement is evaluated by the review group for every application. Once a grant is funded, each Health Scientist Administrator is responsible for assuring that the grant-holder is successful in recruiting and retaining minority subjects. Specific to the mission of the NIDCD, otitis media (ear infection) is one area in which some minority groups may have a greater incidence. The NIDCD is expanding its research of vaccines against otitis media with an emphasis on minorities. In addition, the NIDCD currently funds two National Multipurpose Research and Training Centers (RTCs) with Clinical Trial components. These RTCs have resulted in increased involvement of minority subjects; they have placed special emphasis on attracting African-American, Native American and Hispanic-American subjects.

SUCCESS RATES

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates.

Dr. Snow: The data required to answer this question are collected centrally at the NIH by means of a Personal Data page in each grant application that is removed before the Institute sees the application. The page states: "Upon receipt and assignment of the application by the PHS, this form will be separated from the application. This form will not be duplicated, and it will not be part of the review process. Data will be confidential. . .All analyses conducted on the data will report aggregate statistical findings only and will not identify individuals."

The most recent publication of these data does present findings for fiscal year 1991 to answer the question. There is no reason to believe that significant changes have occurred that would alter the same data if it were available for last year (FY93). Of the qualified research applications received in FY91, less than one percent (.2) were submitted by Hispanic investigators. The success rate was 100 percent for Hispanics compared to 31.3 percent for the NIDCD's overall success rate. The disparity in these success rates probably reflects the small number of applications from Hispanic investigators.

NATIONAL INSTITUTE ON AGING

ALZHEIMER'S DISEASE

Mr. Smith: As a new director with a fresh perspective, what is your view of the present balance in the Institute's research portfolio between Alzheimer's and other aging-related concerns?

Dr. Hodes: Alzheimer's disease (AD) is an affliction which devastates over 4 million older Americans and their families, with national costs conservatively estimated at $100 billion annually. Research on AD is a high priority for the NIA, and deservedly so because of its terrible impact on the members of our society. The current level of resources allocated to research related to AD is, in part, the product of recent Congressional report language directing the NIA to set aside specific amounts or portions of its budget for this purpose.

So often, it is research which is designed to increase our understanding of basic biomedical and behavioral processes which yields the most important breakthrough findings that impact upon specific diseases. Although I agree that research on AD should utilize a significant portion of NIA's attention and resources, preset levels of support for AD research make it more difficult to exercise best scientific judgement regarding appropriate levels of support for NIA's other programs and initiatives.

OLDER AMERICANS' INDEPENDENCE CENTERS

Mr. Smith: What are your views about the future role of the Claude Pepper Independence Centers in the NIA research portfolio?

Dr. Hodes: The Claude D. Pepper Older Americans' Independence Centers (OAICs) are an important part of the NIA's research portfolio. Through the support of clinical and basic research, and the career development of young investigators, these centers offer promise for increasing independence among older Americans in the future. The OAICs conduct research on interventions to help older people continue to live independently and avoid institutionalization or prolonged hospitalization. They also support basic research that is necessary to the development of such interventions. Besides testing specific ways to prevent disability, the OAICs train additional researchers capable of doing such studies, and disseminate information on successful interventions to clinicians and the general public. Studies include:

- New treatment strategies against urinary incontinence in nursing home residents and community-dwelling women.

- The impact of strengthening and aerobic exercise on disability from arthritis of the knee.

- Effectiveness of comprehensive assessment in preventing unnecessary readmissions of hospitalized geriatric patients.

- Ways to prevent or lessen disabilities from respiratory tract infections.

- A home-based rehabilitation strategy for post-hip fractures.

- Interventions to ameliorate the condition of older women with multiple vertebral fractures who have substantial pain, deformity, and disability.

- Prevention of functional decline in older patients during hospitalization for acute illness.

There continues to be considerable interest in the scientific community in the Pepper Centers program. In FY 1994, the NIA intends to fund two additional OAICs which will bring the total to eight OAICs by the end of the fiscal year, and the FY 1995 request would fund a ninth center.

INTRAMURAL PROGRAM

Mr. Smith: Nothing in the 1994 appropriations bill or reports suggested that you reduce funding for your intramural program. Why did you do this when your overall funding increased by $20 million?

Dr. Hodes: The Congressionally imposed limitation on the amount spent for administrative costs impacted severely on our intramural program. The provision limited each agency to no more than the amount requested for administrative costs in the FY 1994 President's Budget. As required by the President's Budget, these administrative cost levels were significantly less than the FY 1993 levels for all NIH intramural programs with the exception of specific increases for research on targeted areas such as AIDS. Since most expenditures within the intramural program are included in the administrative cost category, our flexibility to provide satisfactory resources was diminished. Although we attempted to provide additional funding to the intramural mechanism at the appropriation level, compliance with the administrative cost cap required funding at the same level as the FY 1994 President's Budget.

Mr. Smith: The 1994 House appropriations report encouraged you to increase intramural research in cardiovascular aging. Have you reallocated resources within your intramural program to reflect this emphasis?

Dr. Hodes: Yes. The Laboratory of Cardiovascular Science has received preferential allocation of resources within the resources available to the intramural program.

DEMOGRAPHY OF AGING CENTERS

Mr. Smith: Why have you chosen to add six new demographic research centers in 1994?

Dr. Hodes: For the last several years, NIA has cofunded several National Institute of Child Health and Human Development (NICHD) Population Centers in order to promote research on population aging. While very valuable, this approach has some limitations in terms of what could be supported and the fact that several institutions with research activities on population aging did not have NICHD-supported Centers. Many major research areas, such as long term care and the oldest old population, have suffered because of lack of focussed resources. Following strong encouragement in the FY 1994 House Appropriations language, the NIA issued a request for applications calling for Exploratory Centers on Demography of Aging.

The centers will focus on topics of both national policy interest and high scientific importance. The topics will encompass forecasting life and health expectancy and health and long term care usage, the medical demography of chronic diseases, including the integration of medical demography with population genetics; the costs of aging-related illnesses and disabilities, including those of the last year of life; demographic analyses of the aging of disadvantaged populations including the African American and Hispanic populations; the oldest old population which is the fastest growing component of the population; improving survey methods; intergenerational exchanges; and the determinants and consequences of retirement patterns.

These small exploratory centers will focus upon making several large scale databases available to the research community. The databases include major national longitudinal surveys in which NIA has made major investments over a number of years and which also have important potential for uncovering significant new understanding of the older population relevant to reforming Social Security, Medicare, and monitoring the impact of the Americans with Disabilities Act and Health Care Reform.

GERONTOLOGY RESEARCH CENTER

Mr. Smith: What is the status of the effort to establish a clinical program at your Gerontology Research Center in Baltimore?

Dr. Hodes: We have long standing programs in clinical research at the Gerontology Research Center primarily involving the facilities of the Francis Scott Key Medical Center which are contiguous to our facility and to which many of our physicians/scientists hold adjunct positions. We are continuing our clinical research relevant to hormone replacement therapy, behavioral interventions, prostate disease, the menopause, vascular disease, etc. Such opportunities to explore novel therapies are increasing and will be vigorously explored by our staff. Plans for construction of a new clinical physical facility have been put on hold pending a review of NIH's total intramural program and evaluation of the future of the Clinical Center in Bethesda.

Mr. Smith: Does the Baltimore Longitudinal Study of Aging presently have adequate sample size to draw conclusions about minorities and women? If not, are changes underway to make this possible in the future?

Dr. Hodes: Women were added to the Baltimore Longitudinal Study of Aging (BLSA) in 1978. Most recently, we have added a cohort of women 45-55 years of age to facilitate studies on the medical, physiology and psychological changes that occur during the menopause and which critically affect their risk of disease. This cohort adds the additional participants needed for our current initiatives on women's health. The current composition of the BLSA is not sufficient to support our current initiative in minority health related to vascular disease, hypertension, prostate disease and metabolic disorders. Very active recruitment programs are underway to increase the number of minority participants in the BLSA.

MINORITY HEALTH CENTERS

Mr. Smith: How may exploratory centers for health promotion in minority populations do you presently have? Do you see this effort growing further?

Dr. Hodes: The NIA presently funds, in collaboration with the NIH Office of Research on Minority Health, six exploratory centers for research on health promotion in older minority populations. Two centers are funded directly by the NIA and four are funded by the NIH Office of Research on Minority Health. Within these centers, pilot research on health status and interventions for improving health is being carried out studying African American, Hispanic and Asian/Pacific Islander groups.

NIA is hopeful that these exploratory centers will compete successfully in the NIH application process and develop into full research centers on minority health after this initial three year funding period. The FY 1995 proposed budget supports continuation of this initiative at current levels.

ADEAR CENTER

Mr. Smith: What is the annual cost of the Alzheimer's Disease Education and Referral Center? How many inquiries does it receive?

Dr. Hodes: In FY 1993, the cost for the Alzheimer's Disease Education and Referral Center was $1.2 million. The Center received 25,133 inquiries and distributed 275,000 publications during 1993.

ALZHEIMER'S DISEASE FUNDING

Mr. Smith: Provide a five-year table of funding for Alzheimer's Disease throughout the Department.

Dr. Hodes: The following table depicts funding for Alzheimer's disease for the Department of Health and Human Services:

ALZHEIMER'S DISEASE
(Dollars in thousands)

	1991 Actual	1992 Actual	1993 Actual	1994 Estimate	1995 Estimate
National Institutes of Health:					
National Institute on Aging........	$155,361	$197,080	$202,744	$213,287	$218,000
National Cancer Institute.......	164	501	593	624	634
National Heart, Lung, & Blood Institute.......	292	2,043	1,954	2,056	2,125
National Institute of Dental Research........	396	367	0	0	0
National Institute of Diabetes & Digestive & Kidney Diseases........	1,904	2,000	2,100	2,209	2,300
National Institute of Neurological Disorders & Stroke..........	34,553	38,844	42,266	44,464	46,091
National Institute of Allergy & Infectious Diseases........	1,743	1,558	2,364	2,487	2,568
National Institute of Child Health and Human Development.....	689	713	266	280	280
National Eye Institute.......	122	115	1,444	1,519	1,575
National Institute of Environmental Health Sciences.	303	424	97	102	102
National Institute of Arthritis & Musculoskeletal & Skin Diseases...	1,505	1,758	1,625	1,737	1,809

Alzheimer's Disease (Con't)

National Institute on Deafness & Other Communication Disorders.......	1,085	1,022	1,438	1,513	1,569
National Institute of Mental Health..........	26,205	26,990	24,185	25,443	26,379
National Institute on Alcohol Abuse & Alcoholism......	567	1,027	823	866	750
National Center for Research Resources.......	1,739	1,194	1,911	2,010	2,101
National Institute of Nursing Research........	3,123	3,188	3,369	3,544	3,700
Fogarty International Center..........	52	43	60	63	53
Total, NIH......	229,803	278,867	287,239	302,204	310,036
Health Resources & Services Administration..	0	3,974	4,959	4,959	4,959
Centers for Disease Control & Prevention....	175	178	33	63	63
Substance Abuse & Mental Health Services Administration..	626	277	60	51	51
Agency for Health Care Policy & Research........	500	563	628	645	666
Health Care Financing Administration..	1,400	1,400	1,400	1,500	500
Administration on Aging...........	850	250	300	350	300
TOTAL, ALZHEIMER'S	233,354	285,509	294,619	309,772	316,575

CENTERS

Mr. Smith: Are any Alzheimer's disease centers up for recompetition in either FY94 or FY95?

Dr. Hodes: Nine Alzheimer's Disease Centers were recently reviewed for competing renewal in FY 1994. Ten more Centers will submit renewal applications this year for funding in FY 1995.

Mr. Smith: Identify the number, type and subject matter of research centers supported in 1994.

Dr. Hodes: In FY 1994, the NIA will support 56 centers. Included are 28 Alzheimer's Disease (AD) Centers, 8 Older Americans' Independence Centers (Pepper Centers), 6 Applied Gerontology Centers, 6 Demographic Centers on Population Aging, 2 Exploratory Centers for Research on Health Promotion in Older Minority Populations, 4 Rural Health Centers, 1 Core Center, and 1 Geriatric Research and Training Center (GRTC). In addition, the NIA has 27 Alzheimer's disease satellite sites that complement the Alzheimer's Disease Centers.

The Alzheimer's Disease Centers support the full range of Alzheimer's disease research. These centers support shared resources and facilities for research on AD, allowing a number of investigators, many of which are supported directly by the center grants, to provide a multidisciplinary approach to a joint research effort; or, for researchers from the same discipline to focus on a common research problem. The centers also offer ancillary supportive activities such as protracted patient care necessary to the clinical research effort. Additionally, centers serve as regional resources for special research purposes, such as information dissemination targeted towards health practitioners and other outreach activities. The Alzheimer's disease satellite clinics complement the AD Centers by serving as vehicles to target minority, rural or other underserved populations and enhance the clinical research capabilities of the AD centers through the diversification of the research patient pool.

The Older Americans' Independence Centers were authorized by Congress to conduct research on interventions to help older people continue to live independently and avoid institutionalization or prolonged hospitalization. The Applied Gerontology Centers feature studies of social and behavioral interventions to prevent dependence.

The Demographic Centers on Population Aging, initiated in FY 1994, will apply state-of-the-art demographic, economic and mathematical methods to new databases and assist in the continuation of demographic research utilizing data gained from studies such as the Health and Retirement Survey.

The Exploratory Centers for Research on Health Promotion in Older Minority Populations, established in FY 1993, study health status, health behavior and practices, and interventions for improving the health of older Black, Hispanic, and Asian Americans. The Rural Health Centers focus on the changing sociodemographic and epidemiologic characteristics of the older rural population. The core center provides support for the operation of key epidemiological and demographic studies. The GRTC focuses on increasing the numbers of trained individuals in geriatrics and gerontology.

BIOMEDICAL AND BEHAVIORAL RESEARCH

Mr. Porter: Dr. Hodes, what is the relationship of biomedical research and behavioral research on aging? Are there instances in which both approaches are useful to a given problem?

Dr. Hodes: It should be fully recognized that the biomedical and behavioral aspects of aging have complex interrelations; such interrelationships can be demonstrated for many of the diseases or conditions that afflict persons of all ages. Because of these interrelationships, the NIA encourages and supports studies that approach both the biomedical and the behavioral aspects of aging and the diseases and disabilities commonly associated with aging.

As just one example, the NIA supports a number of initiatives that draw upon both the biomedical and behavioral disciplines with the common endpoints of a reduction in physical frailty and an increase in levels of independence and productivity in older persons. It is a major problem: over 250,000 older persons suffer from hip fracture each year and many more suffer from loss of independence due to compromised strength and mobility. A number of clinical studies just completed have shown that fall rates in moderately frail older persons, living at home, can be reduced significantly by behavioral interventions targeted to either balance, strength, or endurance problems, depending upon the person's deficit. Research has shown that exercise in later life can improve overall quality of life, including significant reductions in perceived stress and anxiety levels. To turn from behavioral to biomedical approaches to this problem, researchers are studying the use of "trophic" factors, including certain hormones, which are needed to maintain muscle, bone, and other tissues. Other research is underway to better understand and modify age-related changes in bone metabolism and bone cell activity. Both the biomedical and behavioral aspects of physical frailty need to be explored in order to best ensure the development of appropriate treatment and prevention interventions.

Mr. Porter: How do you plan to allocate research funding between these two approaches?

Dr. Hodes: The NIA is currently engaged in a collective planning effort to determine scientific areas of maximal need and to identify opportunities. The first phase of this effort was completed last winter; recommendations that have since been developed will be discussed in depth at a summer retreat. Through the identification of appropriate levels of support for various research initiatives, both biomedical and behavioral by discipline, we are working to assure that those resources entrusted to the NIA will be most effectively utilized. Finally, the peer review process yields important guidance by evaluating the relative scientific merit of proposed research, information that will assist NIA in making final funding decisions.

PROLONGING INDEPENDENCE

Mr. Stokes: As the congressional justification states, the aging of our society will impact health care costs, regardless of the means by which these costs are covered. It further states that even with the hope of major advances in the treatment and prevention of debilitating disease, the demand for long-term care is expected to expand dramatically in our society. Doctor, are we making real progress in not just prolonging life, but more importantly prolonging independence and the associated quality of life? Elaborate.

Dr. Hodes: The goal of aging research is not simply to prolong life but to make the remaining years of life as productive and satisfying as possible. To this end, NIA's program of research is designed to develop new methods that can treat and prevent illness and disability, promote independence, and avoid institutionalization. For example, the Institute's Claude D. Pepper Older Americans Independence Centers are testing a home-based rehabilitation program for victims of hip fractures; new treatment strategies against urinary incontinence; and ways to prevent functional decline during hospitalization for acute illness. A coordinated program that combines research on osteoporosis and bone strength, studies to identify risk factors for falls, and training for improved balance, strength, and endurance has discovered ways to reduce costly falls and fractures. Recent discoveries in the NIA Alzheimer's disease program stimulate optimism that therapies can be developed to delay onset and progression of symptoms and dramatically reduce the human suffering and financial burden caused by the disease. Other research is increasing our understanding of cardiac function in older people with the aim of preventing frailty and mortality from heart disease. In collaborative studies with the National Cancer Institute, the NIA seeks to learn more about the impact of cancer in the elderly and to improve screening, diagnosis, and treatment of cancer in older people.

NIA's Women's Health and Aging Study is collecting data on nearly 20 major diseases and conditions, including cognitive impairments and mental illnesses, to determine their presence and severity and how these impact on disability in women age 65 and older. NIA research on long-term care is looking for ways to avoid institutionalization, ease the burdens of family caregiving, and design strategies that meet older people's specific needs. All of these efforts are aimed at the improvement of quality of life and have the potential to reduce the rate of increase in long-term care and, therefore, overall health care costs.

. CLINICAL TRIALS

Mr. Stokes: What are some of the most significant clinical trials underway at your institute? What are the expected benefits to be achieved from this investment?

Dr. Hodes: The NIA supports a group called the Alzheimer's Disease Cooperative Study Unit, a consortium of 33 sites across the country, to do clinical studies in Alzheimer's disease. The unit's first study began in October, 1992 and is a group trial of

Deprenyl and Vitamin E, alone or in combination, versus placebo to determine if either compound alone, or the combination can delay the progression of symptoms and signs in Alzheimer's disease over a two-year period. The expected benefits from any positive clinical trial in Alzheimer's disease would be enormous from a variety of perspectives including the increase in intellectual, emotional, and social well-being of the affected individual and his/her family and caregivers, and the decreased economic and social costs to families and society.

NIA is supporting a clinical trial to test the effectiveness of non-pharmacologic strategies for hypertension in the elderly. Approximately 50 percent of persons between the ages of 60 and 80 are treated with antihypertensive medications. Because drug therapy is associated with a number of side effects that may be especially problematic in the elderly, organizations such as the Joint Committee on Detection, Evaluation and Treatment of High Blood Pressure have recommended nonpharmacologic treatment of hypertension. The overall goal of this research project is to determine whether weight control and/or reduced salt intake can maintain satisfactory blood pressure control in persons aged 60-80 years whose antihypertensive medication has been withdrawn.

Another ongoing clinical trial involves testing different treatments to prevent or reverse loss of bone mass in the hip in persons over age 65. Fractures of the femur are considered the most serious consequence of low bone mass. Hip fractures are a cause of significant disability and mortality in men and women 65 years and older.

Our intramural research program has also increased its clinical research activities. Exciting results have been obtained in administering growth hormone releasing hormone, the natural stimulant of growth hormone production, to older growth hormone-deficient individuals. This factor was able to restore growth hormone production without negative effects observed with administering growth hormone supplements directly, and restored levels of IGF-1, a critical mediator of growth hormone action. Also, potential synergistic effects were noted in combination with sex hormone replacement therapy. Such treatments can now be tested for their ability to reduce frailty, increase mobility and lessen cardiovascular disease in older individuals. Various behavioral interventions are under trial to reduce incontinence in the nursing home session and to increase the strength and mobility of older individuals recovering from hip fracture.

CARDIOVASCULAR DISEASE RESEARCH

Mr. Stokes: Is there extensive collaborative effort between your Institute and the National Heart, Lung, and Blood Institute. In the area of cardiovascular disease research, elaborate. In your Institute what opportunities are on the horizon in this research field?

Dr. Hodes: The NIA and the National Heart Lung and Blood Institute (NHLBI) have a history of collaborative research which is best exemplified by the jointly funded study of Systolic Hypertension in the Elderly (SHEP). This study demonstrated the importance of treating isolated systolic hypertension with blood pressure-lowering agents to prevent strokes. Prior to this study many physicians thought it was unnecessary and perhaps even harmful to older patients to treat this condition. The SHEP study established the stroke-reducing benefit of treating systolic hypertension in older people. Recommendations based on the study are becoming national treatment standards. This collaboration between the two institutes has led to changes in the clinical practice of physicians which should reduce strokes and the accompanying health care costs.

Recently the NIA and the NHLBI signed a Memorandum of Understanding which states that both institutes share an interest and a mandate to support research on cardiovascular diseases in relation to the aging process, and that to avoid redundancy in research programs, they agree to share information on research initiatives on cardiovascular diseases relevant to aging. This should bring collaboration between the two institutes even closer.

NIA currently supports a clinical trial to determine the effectiveness of non-pharmacologic treatment for hypertension, a very common problem in geriatric populations. Hypertension is usually treated with drugs with side effects that are unpleasant and often lead to problems with compliance. The potential value of a non-pharmacologic treatment (weight reduction and salt restriction) could have wide application.

Areas of interest for future research include attempting to understand the role of aging per se in the development of cardiovascular disease.

The NIA intramural research program, located at the Gerontology Research Center in Baltimore, is pursuing cutting edge research on cardiovascular disease and aging. Collaborative studies are being conducted both with extramural scientists and with individuals in the intramural program of NHLBI. At this time common efforts include monitoring heart function in animals following gene therapy to increase vascularization to the heart. It is likely that advantage can be taken of this approach to treat vascular insufficiency and atherosclerosis. Also, nutritional surveys are being conducted on participants in the Baltimore Longitudinal Study on Aging in collaboration with scientists at Tufts and Johns Hopkins University. The levels of various nutrients such as vitamin A, vitamin C and zinc are studied as a function of age, eye disease (cataracts) and dietary intake and will be extended to their relation to cardiovascular disease.

DIRECTION OF NIA RESEARCH

Mr. Stokes: The congressional justification states that the over-85 age group is the fastest growing segment of the American population. In light of this fact, to what extent has the research supported by your institute taken on a new direction?

Dr Hodes: Yes, the over-85 age group is growing very rapidly now, and will increase significantly in size when the baby boom cohort reaches that age. Many NIA researchers are predicting an 85+ population that could far exceed that projected by the Social

Security and Census Projections. Social Security middle range projections (which are the basis for actuarial calculations on the Trust Funds) predict 14.6 million 85+ in 2050 while Census predicts 18.9 million. However, NIA funded researchers have projected that the numbers could range from 27 to 48 million given their estimates of life expectancy increases at advanced ages. The implications of this potential surge in the very old population--centenarian numbers are growing even faster--could be profound for Social Security, Medicare, and Medicaid.

The NIA research program has responded in a number of ways. First the Institute's demography and population epidemiology component increased its collection of longitudinal data on the "oldest old" or over-85 population, about whom very little was known. Based on findings in some of the data bases developed--which included the Longitudinal Study on Aging, the National Long Term care Study, and the Health and Asset Dynamics of the Oldest Old--a special volume was recently published on the oldest old.

Since the 1980's, the Institute has issued a program announcement encouraging research on the oldest old population and established research on this special population as an Institute priority. Resulting research initiatives focussed on a number of issues related to the over 85 population, including estimation of future trends in health and life expectancy. The aim of this research was to produce more scientifically valid forecasts of life and health expectancies of the over-85 population, and thus also of their numbers and demographic composition. The research program emphasizes trends in the population's disability levels, which surprisingly appear to be dropping rather than increasing, and the reasons which could account for this unexpected and potentially remarkable trend. Other important issues include the growing numbers of minority elderly who reach these advanced ages and calculations of their life expectancies, the impact of health and long term costs on family finances, and the heavy costs experienced in the last year of life. Since about two-thirds of those aged 85 and over are women, much of the NIA's program on women's health, such as the Women's Health and Aging Study, is relevant. This study is collecting data on nearly 20 major diseases and conditions, including cognitive impairments and mental illnesses, to determine their presence and severity and how these impact on disability in women age 65 and older. The same holds true for NIA research on functional independence, which explores innovative approaches to minimize institutionalization or hospitalization and disseminates information on successful interventions to clinicians and the public.

NUTRITION

Mr. Stokes: Today, we are learning more and more about the direct relationship between nutrition and disease prevention. How extensive is the research in this area at your institute? Is that research geared toward a specific disease or for the advancement of disease knowledge in general, explain.

Dr. Hodes: The NIA is strongly committed to supporting and promoting nutrition research. In FY 1993 the NIA supported 105 nutrition-related projects with the total research expenditures reaching just over $18 million. Currently our fundamental and applied knowledge of the relationship between nutrition and aging is still very limited. The nutrition research supported by the NIA is geared both toward specific diseases such as osteoporosis, Alzheimer's disease, cancer and coronary heart disease, as well as to examining generalized nutritional and metabolic processes during aging, and understanding of the role of nutrition in maintaining health for successful aging. The ongoing studies range from very basic investigations, such as, the regulation of cellular metabolism and energy production, to clinical studies in hospitalized patients, nursing home residents and free-living elderly. NIA is supporting two clinical studies aimed at maintaining skeletal integrity in older individuals. One study involves an intervention with supplemental calcium, and the other is evaluating the effect of a combined regimen of calcium and vitamin D in the prevention of bone loss in older subjects. The investigations examine both primary malnutrition caused by diet alone and secondary malnutrition arising from factors such as the presence of disease, special physiological states, or inborn errors of metabolism. One specific area of investigation has been the aging model of dietary restriction. Rodent models on regimens of dietary restriction have shown a decrease or delay in the disease processes normally accompanying aging. The NIA is currently trying to elucidate the basic mechanisms responsible for the positive effects of dietary restriction in rodents to determine if these findings can be translated into potential health benefits for humans.

MOLECULAR BIOLOGY

Mr. Stokes: Can you highlight for us what advances would stem from increased investments in molecular biology, as it relates to the diseases and disorders under the purview of your institute?

Dr. Hodes: A major part of basic research is the identification and characterization of normal pathways and processes so as to provide a baseline to understand pathological processes. By way of contrast, study of rare diseases (which perturb normal biological processes) often provides an understanding and insight into normal processes and more common pathologies. One major innovation to result from the practice of modern molecular biology is the ability to identify, isolate and modify genes. As a result of such experimentation one might expect to improve our understanding of disease processes and to identify possible targets for therapeutic intervention.

Advances can be expected from increased investment in molecular biology related to age-related diseases such as Alzheimer's disease and other neurodegenerative diseases, cancer, diabetes, cardiovascular disease, osteoporosis, osteoarthritis, pneumonia, etc. Examples include: 1) An NIA-supported investigator has shown that a unique characteristic of cancer cells is the expression of the telomerase gene. Telomerase prevents the shortening of chromosomes that normally occurs during cell division. If the telomerase gene can be turned off, it is possible that continued replication of cancer cells would be blocked. 2) An understanding of genetic regulation of "programmed cell death" would be useful in developing interventions to retard death of neurons in a variety of neurodegenerative diseases. 3) Transgenically up-regulating the expression of antioxidant defense systems could delay the onset of diseases such as cancer. 4) Regulation of expression of genes for growth factors and growth factor receptors could be used to amplify our ability to respond to stress, e.g. immunological defense against microbial pathogens. All of these strategies would be impossible without a continuing commitment to fund molecular biological research on the diseases of aging.

GENE THERAPY

Mr. Stokes: Gene therapy appears to offer tremendous hope for making significant progress in the treatment of diseases and disorders. In your institute, which major diseases and disorders are offered the most hope through further advances and investments in gene therapy, elaborate briefly. How much is included in the FY 1995 budget request for gene therapy? How much did the Institute invest in this research in FY 1994 and FY 1993?

Dr. Hodes: Research supported by the NIA has made significant contributions to the development of novel gene therapy techniques which may prove to be highly beneficial for the treatment of disorders and diseases associated with human aging. Myoblast-mediated gene therapy (using muscle precursor cells known as myoblasts as the cellular delivery system) offers the advantages of stable, sustained delivery of soluble biological molecules such as human growth hormone or hGH, the growth factor IGF-I, and biologically important factors such as IL-2 to the blood for distribution throughout the body. NIA-supported research has demonstrated that the blood and tissue levels of HGH, IGF-I, and IL-2 show an age-related decline and that the decreased levels may play important roles in the age-related decline in musculoskeletal function, immune function and the age-related diseases osteoarthritis and osteoporosis. Another approach to gene therapy stems from research focussed on the use of a transplantable rat pituitary cell line GH3 to deliver GH to old animals with evidence of significantly decreased levels of blood GH. Restoration of GH to these animals resulted in the restoration of a functional thymus gland and repopulation of the aged bone marrow with cells involved in active hematopoiesis (red and white blood cell formation). Experiments are in progress to assess if this gene therapy-based intervention results in the restoration of good immune function in these old animals. If this experimental intervention results in the improvement or restoration of immune function in these compromised animals, it will pave the way for the design of intervention strategies in humans aimed at improving immune function and protection against infectious diseases in the elderly, a high priority research initiative of the NIA.

Gene therapy for Alzheimer's disease may become a possibility if systems for the delivery of foreign genes to brain cells can be developed. Research leading to the development of such a gene therapy delivery system based on a viral vector is being developed with NIA funding. The identification of specific mutations which lead to early onset familial Alzheimer's disease also opens the way to correction of these defects, should appropriate gene therapy techniques become available.

We have recently established a Gene Therapy Unit to form a focus in the intramural program for such research. At present our intramural program is involved in assessing the ability of gene therapy to deliver needed genes to the cardiovascular system and the brain in experimental animals. The genes for factors that increase vascularization are being administered to the hearts of mini pigs and possible increases in blood flow to the heart are being assessed. Such approaches are intended to supplement angioplasty in improving blood flow to the aged heart. In addition, we are undertaking studies to deliver needed genes to the brain. Using gene therapy vectors expressed in neurons, we have been able to supply certain receptors for neurotransmittors which are lost with age. Also, we are testing the ability of gene therapy to deliver needed factors to areas of the brain involved in strokes, at this time in experimental animals.

In FY 1993 the Institute spent $1,459,000 for gene therapy research; FY 1994 and 1995 estimates are $1,500,000 for each year.

EMPHASIS IN MINORITY HEALTH

Mr. Stokes: With regard to diseases and disorders that affect minorities, what are the most significant areas of research that are supported and conducted by your Institute?

Dr. Hodes: During the last several years NIH has supported research on frailty in minority populations, including examination and identification of risk factors that lead to frailty as well as development and testing of interventions to prevent or lessen impairment in functioning. Research is also supported on cardiovascular disease in older minority individuals, including hypertension and stroke, conditions prevalent in African American and Hispanic groups.

Research on Alzheimer's disease, which has received long-standing emphasis in NIA, has begun to include more of a focus on the incidence and course of the disease in older minority groups. The NIA-supported Alzheimer's Disease Research Centers and the associated satellite clinics, which serve to increase the involvement of minority groups, conduct basic, clinical and behavioral research related to Alzheimer's disease.

Considerable research is supported on behavioral and social aspects of minority aging, including family relationships and support networks, especially as related to family caregiving in long term care. Research is also supported on health attitudes and health promotion in older minority groups. Several research projects focus on the impact of participation in physical activity programs on health status.

Mr. Stokes: As the director of an institute of the NIH, the Nation's principal federally-supported biomedical research investment, how would you respond to the statement, the minority health crisis continues--while we continue to witness an unprecedented explosion in scientific knowledge and a phenomenal capacity to treat and cure disease, and while medical and technological breakthroughs are affording Americans a longer life expectancy? Please elaborate.

Dr. Hodes: The NIA is well aware that many minority populations bear a disproportionate burden of illness. For example, despite the fact that the Hispanic population has a life expectancy approximately 3 years longer than the total population (79.1 for Hispanics and 75.4 for the total population in 1990), the years of healthy life for Hispanics are only 0.8 years more than the overall population (64.8 for Hispanics and 64.0 for total population in 1990). Years of healthy life take into consideration not only the life tables but indicators of morbidity as reported by activity limitations and self-reported health status from the National Health Interview Survey. Thus the quality of life for Hispanics, particularly in their later years, indicates some disproportionate dysfunction. African-Americans suffer disproportionately from hypertension and certain types of cancer.

Special initiatives on the health and well-being of minority populations have therefore been implemented in all areas of aging research. For example, a special network of community outreach satellites of Alzheimer's disease centers has been established to recruit patients from minority and underserved populations. The Institute has launched a multifaceted initiative on the health implications of the menopause and hormonal changes which has a focus on minority women. A new component of NIA's intramural Baltimore Longitudinal Study of Aging will research prostate disease and hypertension and other disorders which affect minority individuals disproportionately. NIA is expanding research on long-term care patterns and prevention of frailty in African-American, Hispanic, and other minority populations. In collaboration with the NIH Office of Research on Minority Health, NIA supports exploratory centers for health promotion and minority aging, including the development of interventions and community outreach programs.

AGING RESEARCH

Mr. Stokes: What are some of the most exciting and most promising basic and clinical research opportunities at your institute, elaborate on the benefits to be achieved from further investments in this research?

Dr. Hodes: Findings from basic research allow subsequent rational development of breakthroughs in detection, treatment, and prevention interventions that benefit all sectors of our society. One of our initiatives in basic research is to develop an understanding of the genetic basis of aging and longevity. Research supported by this initiative makes use of state-of-the-art techniques in cellular and molecular biology to identify and characterize genes which play an important role in determining longevity. Information gained from understanding the fundamental mechanisms of aging at the cellular level is an important first step in the design of effective interventions to delay or postpone the functional declines associated with aging and thus improve the quality of life in our later years. We are now close to identifying and isolating the gene which causes Werner's syndrome, a disease that has many features of premature aging. Information gained from this work should help us understand more of the genetic basis of aging and form the basis for the design of research studies for treatments to increase healthy lifespan.

Alzheimer's disease (AD) is a very high research priority for NIA. This disease currently affects an estimated four million Americans and costs the nation at least $100 billion each year. A major recent finding from NIA-supported research demonstrated that a variation of the apolipoprotein E (ApoE) gene, ApoE4, is associated with an unexpectedly high number of AD cases and is potentially a major risk factor for developing AD. Additional large population-based studies are necessary to confirm the association of ApoE4 with AD. NIA will channel resources into the elucidation of the molecular pathways of this disease, with a focus on the role of ApoE4. If ApoE is found to play a causal role in AD, this information would lead to the subsequent design of optimal treatment and prevention strategies to lessen AD's tremendous personal and economic burden.

It is important to maintain a balance between basic and applied research, quickly utilizing knowledge gained from basic studies in the design of clinical studies to develop new detection and treatment interventions. We will pursue studies to clarify the effects of anti-inflammatory agents and estrogen replacement on the incidence and progression of AD; preliminary studies have suggested that these agents could be responsible for lowering the risk for AD. Regarding research on care for those with AD, current studies are accumulating and evaluating data on existing Special Care Units, to determine the effectiveness of these units as compared to other methods of care for AD patients.

Gene therapy has extraordinary potential for amelioration of diseases and conditions including those that are of particular concern to older Americans. As the precise biochemical defects responsible for cardiovascular or central nervous system diseases are determined, gene therapy could provide technology that would not only be effective, but also relatively low-cost when contrasted with the present treatment and long-term care alternatives. Truly decisive technologies get at the underlying causes and mechanisms of disease. However, today with nursing homes, respirators, and intensive care units for the very old, we are dealing with halfway technologies for many of the disabilities and diseases of the elderly which place an unusually high financial burden on the health care system. NIA's intramural research team will continue to pursue its cutting edge research on atherosclerosis and cardiovascular disease with a focus on developing appropriate gene therapy.

Ongoing clinical studies have been testing strategies for reducing physical frailty. Preliminary results have shown that not all interventions to reduce physical frailty and frequency of falls work equally well; follow-up studies will be designed to identify those interventions that are effective in extending independent life-span. Osteoporosis, a major contributor to frailty, affects over 25 million Americans, mainly women, and is a serious public health problem because associated fractures are a major cause of disability in older people. Costs associated with hip fractures exceed an estimated $7 billion annually. Recently, attention has focused on treating conditions such as osteoporosis and muscle atrophy through replacement therapy with "trophic" factors. These factors promote growth and maintenance of tissues such as bone, muscle, and cartilage. NIA will focus upon this research as well as basic studies to understand and modify age-related changes in bone metabolism and bone cell activity.

In the summer of 1994, NIA will fund a series of studies in a cooperative agreement on the role of menopause in women's health and aging. These studies will enhance understanding of the role of menopause in chronic diseases such as osteoporosis, cardiovascular disease and urinary incontinence, as well as an understanding of why some women experience symptoms while others do not. Improved knowledge is essential in formulating strategies to prevent these diseases or conditions and to ameliorate symptoms and thus improve the quality of life in middle-aged and older women. We currently know very little about the transition from pre- to postmenopause in non-Caucasian racial ethnic groups such as African-Americans, Asians, Native Americans, Hispanics, etc. The funded studies will place a heavy emphasis on obtaining new information in many of these understudied populations.

Behavioral variables, such as the circumstances surrounding the retirement decision, have a profound effect on the health and independence of older persons and their families. Building upon the Health and Retirement Survey beyond the initial five year study will allow accumulation of data on subsequent life events that significantly effect the well-being of the retiree. NIA will continue its efforts to oversample minority populations in this study. New studies of self-care, how and why older people handle their own health needs, has potential for interventions that encourage appropriate health choices and behaviors outside of the costly medical care system. Other research drawing upon behavioral science has shown that cognitive function can be improved through properly designed interventions. Building from findings in laboratory studies of cognitive functioning, behavioral research is developing field studies that could improve the lives of older people in everyday situations. Practical benefits and cost savings may result from, for example, fewer car crashes (vision studies), greater independence (improved self-management of finances) or reduced formal medical care (better medication compliance). The NIA plans such studies as a scientific opportunity to move from theory to ways to maintain and improve cognitive functioning among older people.

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of your Institute?

Dr. Hodes: Substantial numbers of well-qualified students are eager to begin research careers in aging. Funding is available for a number of these students, though undoubtedly, increased funding would further secure the pipeline. Serious attention needs to be paid to ensuring that the most up-to-date and appropriate technologies remain available for them. Equally serious attention must be given to ensuring that adequate opportunities for research careers are maintained.

An adequate pipeline for research requires students of diverse cultural and ethnic backgrounds who are willing and able to be trained in the discipline; funding to support them throughout their training; adequate facilities so that they may be exposed to the most up-to-date technologies; and appropriate opportunities for them once training is complete to ensure that they can use the skills they have learned, and the enthusiasm that they feel, for work on aging.

To maintain that competitive edge, America must also be sensitive to the changing nature of the national and global population. Population aging is among the most profound and widespread of these changes. Therefore researchers need to be trained to address the problems created by this dramatic shift in age. Such researchers can identify technologies that particularly benefit older people and can seek cures and remedies for age-related diseases and impairments. Apart from benefitting the health and independence of older people, the resulting products and services may provide a competitive edge in several industries and service sectors.

MINORITY HEALTH

Mr. Stokes: Please describe the measures your Institute takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported.

Dr. Hodes: In 1988 the NIA established a staff working group on minority aging with representatives from program areas and across the Institute to provide advice on research and training programs focusing on minority health and training of minority investigators. In addition, a subcommittee on minority aging of the National Advisory Council on Aging has been established to provide continuing advice to the Director regarding minority initiatives. These two groups, along with program staff, assist in the development and implementation of strategies in minority health and aging and minority training.

A series of regional workshops sponsored by the NIA working group on minority aging was begun in 1993. Each of the regional workshops focuses on a specific racial or ethnic minority group and provides input on diseases/disorders, and behavioral and social conditions which are important to improving minority health status. The first regional workshop was held in Atlanta, Georgia and focussed on the African American population and Historically Black Colleges and Universities; the second workshop was held in Los Angeles, California and focussed on the Hispanic population;

and the third workshop was held in Albuquerque, New Mexico and aimed to focus on the American Indian population.

A newsletter which reports on NIA minority research and training activities was initiated in the Fall of 1993. The newsletter provides increased dissemination of information and will contribute to increase interactions among programs and investigators. Subsequent editions of the newsletter will report on findings from research grants related to minority health.

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your institute?

Dr. Hodes: The NIA has several initiatives in minority health research and research training which have increased substantially the amount of the NIA budget expended in support of minority programs. The amount expended in FY 1990 was approximately $5 million and increased to $27 million in FY 1993.

The health research initiatives include an emphasis on preventing frailty in minority populations, increasing our knowledge of risk factors for diseases/disorders in older Hispanics, increased research on support networks and long term care, and means of promoting health in older minority groups. Also, NIA has intramural initiatives relating to increased understanding of perimenopausal and menopausal conditions in older African American women, and in increasing the number of minority participants in the Baltimore Longitudinal Study of Aging, so that the study population is more reflective of the general population.

The satellite diagnostic and treatment clinics were established to increase the heterogeneity of the research patient pool and to enhance the research capabilities of the Alzheimer's Disease Centers. The satellite clinics serve as vehicles for the recruitment, diagnosis and management of Alzheimer's disease patients and their families, who are then offered the opportunity to participate in research protocols and clinical drug trials. These clinics are targeted to minority, rural or other underserved populations.

Research training initiatives include the establishment of a Minority Dissertation Research award designed to support the research of new minority investigators and to encourage individuals from a variety of disciplines and programs to study problems in aging; a program of research supplements to current NIA research grants to support the involvement of underrepresented minorities in research, including supplements to awardees who represent demonstrated research expertise over long periods of time and who can be excellent role models for new investigators; and a program of traineeships to minority students enrolled in academic programs leading to a doctoral degree in psychology with a specialty in gerontology. The latter program, administered by the American Psychological Association, is viewed as a model program to determine the feasibility of professional organizations to assist in the recruitment of minority students to research careers in aging.

Mr. Stokes: How does your institute identify its priorities for investments in minority research and research training?

Dr. Hodes: The NIA receives input from a number of sources regarding identification of priorities in minority research and research training. Among the sources are NIA-sponsored research conferences, including those that focus on minority health research and training, as well as conferences which focus on other substantive topics in research on aging. Consultations with researchers in aging also provide input into identification of research priorities. Such staff consultations occur throughout the year, but also occur in depth once a year in connection with program reviews that take place at the time of the meetings of the National Advisory Council on Aging. The Council has a subcommittee established to provide continuing advice regarding minority initiatives. Input is also received from professional organizations.

The staff working group on minority aging, established in 1988, also provides input into minority research and training initiatives. The group, which has representation from each major component of the Institute, is therefore in a position to make recommendations regarding Institute-wide initiatives. A series of regional workshops sponsored by the NIA working group is a source of input on minority research and training initiatives. Each of the regional workshops focuses on a specific racial or ethnic minority group and provides input on diseases/disorders, and behavioral and social conditions which are important to improving minority health status.

MINORITY STAFFING

Mr. Stokes: How many GS-15 and above positions are there in your Institute? How many employees in your Institute are in GS-15 and above positions? In your Institute, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your Institute, how many African Americans are among cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze? If so, what was the response? If the freeze were lifted, how would it help the EEO problem in your Institute?

Dr. Hodes: Currently, the Institute has 58 positions which are filled by employees at the GS-15 and above level. There is one African American female in a GS-15 position, who is Assistant Director for Special Programs.

NIA has no cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level. The NIH has requested relief from the freeze and has been informed that a decision will be made in the near future. If the freeze were lifted, employment of any recruited and selected minority would be facilitated.

MINORITY SUPPLEMENT AWARDS

Mr. Stokes: I understand that a number of the Institutes make minority supplement awards, and that these awards help to increase the success with which minorities compete for research project grants. How long has this mechanism been in place? Since its inception, how many minorities participating in the program have gone on to successfully compete for research project grants?

Dr. Hodes: The NIA has participated in the minority supplement program since its inception in 1989. Because many of the supplement awards funded in earlier years are still active, and because many supplements are awarded to high-school, undergraduate, and graduate students who would not yet be expected to apply for independent research funding, the database for judging who among earlier supplement awardees have received independent support remains small. Nevertheless three former NIA supplement awardees are now funded as principal investigators with research project grants in aging. Others are working as co-investigators in multi-project grants. Their success is an early encouraging sign that the program is achieving its purpose.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of Historically Black Colleges and Universities in biomedical research?

Dr. Hodes: Major initiatives underway at NIA to increase the participation of Historically Black Colleges and Universities (HBCUs) in Institute programs include the following:

- A series of regional workshops which provide information on NIA minority programs and assistance in accessing these programs. Invitations to participate in these workshops are extended to institutions with large minority enrollment, including HBCUs located in the region of the workshop.

- Research supplements to NIA grants in support of minority researchers often provide opportunities for student and faculty from HBCUs to participate in NIH-sponsored research, and may lead to development of independent researchers who can apply to NIA for support.

- Annually NIA has held a workshop known as the Summer Institute in Research on Minority Aging. Participants in the workshop are new researchers interested in research on minority aging. Announcements of the workshop are regularly sent to HBCUs, and several participants have been from HBCUs.

- A program of satellite clinics associated with NIA-supported Alzheimer's Disease Research Centers provides opportunity for HBCUs to collaborate with the Alzheimer's Centers. The satellite clinics were established to increase the involvement of underserved populations, such as rural and minority populations. Although not directly funded, HBCUs are involved in some of the satellite clinics and bring to this collaboration existing interactions with the minority communities.

BIOTECHNOLOGY

Mr. Stokes: Explain why increased research in biotechnology is vital to furthering advances stemming from research under the purview of your institute?

Dr. Hodes: The biotechnology field, by utilizing state-of-the-art genetic engineering and molecular biology techniques, is critical for the development and production of new agents for the diagnosis, treatment, and even prevention of many diseases and disabilities associated with aging. Within NIA's intramural research program, scientists are assessing the ability of gene therapy to deliver needed genes to the cardiovascular system and the brain in experimental animals. The genes for factors that increase vascularization are being administered to the hearts of mini pigs and effects on blood flow to the heart are being assessed. Such approaches are intended to supplement angioplasty for improving blood flow to an aged heart. Also using animals, we are testing the ability of gene therapy to deliver needed factors to areas of the brain involved in strokes, or in other studies, to supply certain receptors for neurotransmittors which are lost with age. These examples of work performed in NIA's own laboratories are but two examples of the exciting and highly promising work that tomorrow's technology could deliver.

MINORITY SUPPORT

Mr. Stokes: What is the present level of support provided to minority institutions by your Institute?

Dr. Hodes: The NIA supports numerous specific initiatives to bring minority investigators into the field of aging research. These initiatives include:

- The establishment of a Minority Dissertation Research award designed to support the research of new minority investigators and to encourage individuals from a variety of disciplines and programs to study problems in aging.

- A program of research supplements to current NIA research grants to support the involvement of underrepresented minorities in research, including supplements to awardees who represent demonstrated research expertise over long periods of time and who can be excellent role models for new investigators.

- A program of traineeships to minority students enrolled in academic programs leading to a doctoral degree in psychology with a specialty in gerontology. This program, administered by the American Psychological Association, is viewed as a model program to determine the feasibility of professional organizations to assist in the recruitment of minority students to research careers in aging.

- Staff visits to institutions with large minority enrollment to discuss NIA programs and to offer technical assistance to applicants.

- A series of regional workshops which provide information on NIA minority programs and assistance in accessing these programs. Invitations to participate in these workshops are extended to institutions with large minority enrollment located in the region of the workshop.

- Annually NIA has held a workshop known as the Summer Institute in Research on Minority Aging. Participants in the workshop have been new researchers interested in research on minority aging. Announcements of the workshop are regularly sent to institutions with a high population of minorities.

- A program of satellite clinics associated with NIA-supported Alzheimer's Disease Research Centers provides opportunity for minority institutions to collaborate with the Alzheimer's Centers. The satellite clinics were established to increase the involvement of underserved populations, such as rural and minority populations.

- The newly established Exploratory Centers for Research on Health Promotion in Older Minority Populations will provide additional opportunities to minority institutions for collaboration. These centers were initiated to study health status, health behavior and practices, and interventions for improving the health of older Black, Hispanic, and Asian Americans.

Mr. Stokes: Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by Historically Black Colleges and Universities in the Institute's programs and activities.

Dr. Hodes: Several efforts are undertaken to increase participation of HBCUs in NIA programs and activities. These efforts include:

- Staff visits to HBCUs and institutions with large minority enrollment to discuss NIA programs and to offer technical assistance to applicants.

- A series of regional workshops which provide information on NIA minority programs and assistance in accessing these programs. Invitations to participate in these workshops are extended to institutions with large minority enrollment, including HBCUs located in the region of the workshop.

- Research supplements to NIA grants in support of minority researchers often provide opportunities for student and faculty from HBCUs to participate in NIH-sponsored research, and may lead to development of independent researchers who can apply to NIA for support.

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- A program of satellite clinics associated with NIA-supported Alzheimer's Disease Research Centers provide opportunity for HBCUs to collaborate with the Alzheimer's Centers. The satellite clinics were established to increase the involvement of underserved populations, such as rural and minority populations. Although not directly funded, HBCUs are involved in some of the satellite clinics and bring to this collaboration existing interactions with the minority communities.

Mr. Stokes: Explain the proposed funding for the programs of your Institute designed to increase the participation of underrepresented minorities in biomedical research and research training.

Dr. Hodes: The NIA participates in all NIH-wide programs to increase the participation of minorities in health-related research and supports several specific initiatives to increase recruitment and training of minority researchers in aging.

NIA's allocation for the combined minority supplement programs offered by NIH (High school, undergraduate, graduate student, postdoctoral associate and minority investigators) in fiscal year 1994 is $1.4 million. The Institute has experienced substantial growth in the number of applications received for this program. We anticipate being able to pay approximately 70 percent of these applications.

The FY 1994 allocation for NIA's program to provide dissertation support to minority students is $600,000. We have received 29 applications for this program this year. As with minority supplements, that number represents a substantial increase from previous years. The Institute anticipates paying approximately 50 percent of these applications.

NIA also provides funds to senior and outstanding researchers on aging to enable them to recruit promising minority students and investigators quickly to their research programs. The Institute provides additional money to training grants in order to train additional minority graduate students and postdoctoral fellows who have been judged qualified. Finally, the Institute is planning to conduct workshops and training sessions for minority investigators who have applied for funding but whose application did not receive a sufficiently high percentile to obtain funding.

ALZHEIMER'S DISEASE

Mr. Hoyer: Several months ago, I met with Dr. Allen Roses of Duke University who has, as you know, been conducting some fascinating research that could lead to a way of diagnosing Alzheimer's disease. Could you give the committee a status report on that research? Is it being funded by NIA?

Dr. Hodes: ApoE4, a variant of a blood protein whose gene is located on chromosome 19, has been shown by Dr. Roses and others to be associated with an increased risk of Alzheimer's disease (AD). The association of ApoE4 with increased risk of AD is dramatic in members of some families in which late-onset AD is inherited. However, in the general population, the association is not quite so clearcut. ApoE4 individuals appear to be at somewhat increased risk for AD. However, a large proportion of AD patients do not carry the ApoE4 gene, and there are many ApoE4 octogenarians who do not suffer from the disease. For this reason, ApoE typing should not be interpreted as diagnostic. Nevertheless, the usefulness of having identified the first AD susceptibility gene cannot be overemphasized. Scientists can now begin to discriminate between the effects of ApoE in the epidemiology of AD and other, possibly environmental, causes. In addition, researchers may be better able to explain the biochemical pathways that result in AD by determining the role of ApoE4 in AD pathogenesis. Perhaps when more is known about its role in AD, ApoE typing may have some diagnostic utility in conjunction with other, as yet unidentified, risk factors. Research on the role of ApoE in AD has accelerated tremendously in the last year. The NIA has funded the studies by Dr. Roses and colleagues through the Alzheimer's Disease Research Center grant to Duke University. Dr. Roses' research has also been supported by his Leadership and Excellence in Alzheimer's Disease award, a seven year grant from the NIA. The NIA supports major projects on the pathobiology and epidemiology of ApoE in AD in several other laboratories as well. Numerous new applications for grants in this area of research are presently under review.

Mr. Hoyer: In last year's committee report, we encouraged the development of a long range plan to slow the progression of Alzheimer's. Would you report on the status of that plan?

Dr. Hodes: The date for the first research planning meeting is May 24-27, 1994. NIA staff have identified approximately 40 scientists representing different disciplines, scientific perspectives and methodological expertise as participants in this research planning exercise. A document has been prepared which provides an historic perspective of AD research and a conceptual framework for future research directions. This document is intended to serve as a starting point to stimulate the participants to think about research opportunities, identification of technical and scientific problems which need solutions, and the need for future research resource needs. Each participant has been asked to submit a brief position paper responding, criticizing or commenting on the document sent to them. These position papers were due by the end of April. They will be reproduced and distributed to all participants prior to the May meeting. The May meeting will be devoted essentially to discussion, debate and the drafting of consensus position papers.

Not all participants in this planning exercise will necessarily have to attend the meeting. Nevertheless, a serious attempt is being made to have a wide range of views represented in the development of a scientific agenda to implement a long range plan for Alzheimer's research. Implementation of this plan will have to follow the development of a scientific agenda which could become the topic of a future joint meeting among scientists from academia, industry, and government in developing coordinated strategies for drug discovery and clinical studies.

In keeping with the spirit of the Congressional language, the National Institute of Nursing Research (NINR), the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS) are being included in this and subsequent meetings and we will be continuing to solicit the help of these Institutes.

The primary focus of the first research planning meeting will be the identification of scientific opportunities and road blocks to the progress of research, all aimed at accelerating the process of discovering effective treatments. Since at the basic science level, the issues of etiology, biology markers, risk factors and targets for correcting the signal transduction pathway are interlinked, participants will address these issues in one meeting.

The second meeting, planned for this summer, will be devoted to research opportunities related to the management of the behavioral symptoms of AD such as agitation, wandering, sleep disturbance, verbal and physical aggression, dressing, and toileting. This meeting is currently in the planning stage, and NIA will be working closely with NINR on this meeting.

A third meeting tentatively scheduled for late summer or early fall will be directed toward prevention issues and how contributions and methodology of epidemiological studies on AD can provide a framework for addressing issues of prevention of AD.

HISPANICS AND NIH

Mr. Serrano: Dr. Hodes, as you know, I raised questions with Dr. Varmus regarding Hispanic hiring and promotion at NIH, Hispanic health research, and Hispanics in biomedical research. I intend to follow up by asking each Institute Director who appears before the Subcommittee to answer this series of questions. First, I would appreciate your telling the Subcommittee what steps you are taking or plan to take to increase Hispanic hiring and promotion within your Institute?

Dr. Hodes: Opportunities for career development and training are being provided to all Hispanic employees at the Institute, with the goal of providing promotion opportunities. Target recruitment is being planned to recruit more Hispanics into positions at the Institute, with special emphasis placed on recruiting Hispanics into postdoctoral and tenured positions. In March 1994, NIA staff organized a forum in New Mexico to contact the science faculty of universities with high Hispanic enrollment which will provide a network of persons to contact when positions become available. Forums of this type will be continued on a regular basis in areas where there are a substantial number of minorities.

HISPANIC HEALTH

Mr. Serrano: Second, what percentage of your budget is directed specifically at Hispanic health issues (with the understanding that much of your research will impact Hispanic health without being directed at Hispanics)?

Dr. Hodes: In FY 1993, NIA support for minority aging was $27.6 million. Approximately one-third of that amount, $9 million, was directed specifically toward Hispanic health issues. The $9 million figure represents two percent of the Institute's total budget.

Mr. Serrano: Third, what programs does your Institute support to increase the participation of Hispanics in biomedical research, including outreach to create a pre-university pipeline?

Dr. Hodes: The NIA participates fully in all NIH intramural and extramural programs directed at increasing the participation of Hispanic and other minorities in health-related research. NIA also supports several Institute specific initiatives to increase minority participation in aging research. For the NIH minority supplement program, in the most recent full year of funding, 19 out of 69 minority supplements were paid to students and investigators who identified themselves as Hispanic. Interest in this supplement program has increased substantially. The Institute is projected to receive approximately 30 percent more applications this year than last. The program includes support for high-school students as a means of increasing the pre-university pipeline into biomedical research.

Among NIA specific programs aimed at recruiting and training minority researchers in aging, 6 out of 25 awards that provide dissertation support have been to students self-identifying as

Hispanic. The Institute also offers extra predoctoral and postdoctoral training slots on training grants in aging research, and provides funds to leaders in research on aging so that they may quickly recruit minority students and investigators to their research programs. Hispanic and other minority students are actively recruited to these slots.

The Institute is also working to assist Hispanic and other minority investigators who are already interested in aging research. Institute staff are organizing a series of workshops in different regions of the country targeted to minority groups. In November 1993 one such workshop, conducted in Southern California, succeeded in attracting a substantial number of investigators identifying themselves as Hispanic. These workshops teach investigators about the grant opportunities available from NIA and provide Institute contacts for the investigators to discuss questions about their work and the process of review and funding of grants. The Institute is now seeking approval to begin a program to assist minority investigators who have already applied to NIA and whose initial application does not receive a high enough score to be funded. This program will assist these investigators with the process of rewriting the application and responding to the initial review.

In addition, NIA is currently funding a $2.5 million research initiative on the health, mental health and social status of Hispanic elderly. Each of the five funded projects has a number of Hispanic researchers associated with it, ranging from one principal investigator to pre- and post-doctoral research associates.

Mr. Serrano: Fourth, what is your Institute doing to recruit and retain more Hispanics for clinical trials?

Dr. Hodes: The NIA supports a group called the Alzheimer's Disease Cooperative Study Unit (ADCSU), a consortium of 33 sites across the country, to do clinical studies in Alzheimer's disease (AD). The ADCSU utilizes the patient resources of the Alzheimer's Disease Centers to provide most of the patients for these studies. Enrollment of Hispanic subjects in the Alzheimer's Disease Centers is progressing steadily. In the last reporting year (1992) there were approximately 540 Hispanics enrolled by the various centers. Satellite Diagnosis and Treatment Centers designed to attract research subjects from underserved communities have been established at many of the Alzheimer's Centers. In particular, the Center at Columbia University in New York serves a predominantly Hispanic community in the Washington Heights neighborhood of Manhattan and the Center in San Diego has a satellite clinic serving Hispanics living in the Imperial Valley, California.

The ADCSU's first study began in October, 1992 and is a group trial of Deprenyl and Vitamin E, alone or in combination, versus placebo to determine if either compound alone or the combination can delay the progression of symptoms and signs in AD over a two year period. This was the first AD clinical study to specifically enroll Spanish speaking individuals, and individuals of Hispanic origin constitute approximately 4 percent of the population enrolled in the study which is slightly larger than the percent of Hispanics 65 years old and older in the U.S. population. In addition, in order to specifically recruit more Hispanics into AD clinical trials, the ADCSU will shortly be initiating a study of the use of new neuropsychological instruments designed to detect AD and assess the effects of drugs over time in clinical trials. For this study, all the instruments have been translated into Spanish, and a group of 150 Spanish speaking individuals with AD will be specifically recruited to evaluate these instruments. In these studies, an extra effort is being made to recruit and retain Hispanic individuals by going to their homes for testing when possible, instead of requiring them to come to the medical centers. Through these efforts, the ADCSU is attempting not only to make an extra effort to recruit Hispanics (and other minority and ethnic groups) into clinical trials, but to evaluate, for scientific reasons, whether there are differences among these groups which could interact with other risk factors for AD or be associated with excess disability.

Mr. Serrano: Finally, at Chairman Smith's suggestion, I should ask what percentage of the qualified research applications you received last year were submitted by Hispanic investigators, how their success rate compared to the Institute's overall success rate, and whether there is an explanation for any disparity in these success rates?

Dr. Hodes: In the last complete fiscal year, the success rate for competing applications was 23.1 percent. Of the ten applicants who self-identified as Hispanic, one was funded yielding a rate of ten percent. The Institute is engaged in a number of efforts to increase the numbers of qualified Hispanic investigators interested in aging research in order to increase their participation in research and to increase their success rate. These efforts include participation in the NIH minority supplement program; issuing a request for applications twice annually that is designed to support dissertation research on aging among minority students; allowing existing training grants to recruit additional minority candidates to training programs; targeted outreach efforts by Institute staff designed to attract Hispanic and other minority investigators to aging research; and a program that permits the most senior and distinguished researchers in aging to quickly recruit qualified minority candidates to their research programs.

HISPANICS

Mr. Bonilla: How is the recruitment of Hispanics for the dementia studies for NIA's Alzheimer's Disease Research Centers program progressing?

Dr. Hodes: Enrollment of Hispanic subjects in the Alzheimer's Disease Centers is progressing steadily. In the last reporting year (1992) there were approximately 540 Hispanics enrolled by the various centers. Satellite Diagnosis and Treatment Centers designed to attract research subjects from underserved communities have been established at many of the Alzheimer's Centers. In particular, the Center at Columbia University in New York serves a predominantly Hispanic community in the Washington Heights neighborhood of Manhattan, and the Center in San Diego has a satellite clinic serving Hispanics living in the Imperial Valley, California. We anticipate that the numbers will grow in these and other Alzheimer's Centers now that screening instruments are being translated into Spanish and will be validated for cultural diversity.

TUESDAY, APRIL 26, 1994.

NATIONAL LIBRARY OF MEDICINE

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

NATIONAL CENTER FOR RESEARCH RESOURCES

JOHN E. FOGARTY INTERNATIONAL CENTER

WITNESSES

HAROLD E. VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DONALD A.B. LINDBERG, M.D., DIRECTOR, NATIONAL LIBRARY OF MEDICINE

FRANCIS S. COLLINS, M.D., PH.D., DIRECTOR, NATIONAL CENTER FOR HUMAN GENOME RESEARCH

PHILIP E. SCHAMBRA, DIRECTOR, JOHN E. FOGARTY INTERNATIONAL CENTER

JUDITH L. VAITUKAITIS, M.D., DIRECTOR, NATIONAL CENTER FOR RESEARCH RESOURCES

WILLIAM BELDON, DIRECTOR, DIVISION OF BUDGET, OFFICE OF THE SECRETARY

Mr. SMITH. The next panel, we have four on this panel.

INTRODUCTION OF WITNESSES

Dr. VARMUS. Thank you, Mr. Chairman. I am sorry to have been a moment late for the first part of this afternoon's session but allow me to present my colleagues who are here at this panel.

On my far right, Dr. Donald Lindberg, who is the Director of the National Library of Medicine; Dr. Francis Collins, on my right, who is the Director for the National Center for Human Genome Research; on my immediate left, Dr. Judith Vaitukaitis, the Director of the National Center for Research Resources; on my far left, Dr. Philip Schambra, the Director of the John E. Fogarty International Center for Advanced Study in the Health Sciences. We will start on my right with Dr. Lindberg.

OPENING STATEMENT

Dr. LINDBERG. Mr. Chairman and members of the panel, I am pleased to tell you that the medical profession is making more and more use of modern information technology, including the much publicized high-speed information superhighway. This is particularly important at a time when the Nation is undergoing a kind of soul searching on the basic tenets on how we obtain health care.

The National Library of Medicine is encouraging U.S. medical institutions to gain access to the Internet. This is the prototype of the "information superhighway" of the future.

The library, that is to say our library, offers access grants to medical institutions, including small hospital libraries, to help them to hook up and to learn how to use these new services. In fact, our entire catalog is now available over Internet.

Mr. Chairman, an increasing number of American physicians now search NLM MEDLINE and other computer databases for themselves, using our user-friendly Grateful Med computer program. These physicians and scientists, too, thus have 24-hour access to MEDLINE and the other NLM databases.

With your permission, I would like to read a little bit from a Times newspaper article that concerns NLM, and the use of the MEDLINE searching program, Grateful Med. This indicates the doctors involved in the article didn't know how to do the searching themselves but they had access to a circuit riding medical librarian who conducted the search and helped come up with the diagnosis for them. A diagnosis for an otherwise very hard to diagnose patient.

I should tell you in this case the Times is the Watertown, New York, Daily Times. I will quote from their article. "Medical professionals are occasionally faced with difficult diagnoses. About six weeks ago, Watertown internist Colin Kellogg had a stumper.

"The patient was in his twenties, healthy and athletic. Dr. Kellogg noticed every time the patient exercised an unusual thing happened. One-half of the patient's face would turn beet red, the other chalky white. The redness would extend exactly down the middle of the patient's face and chest and could include one arm, while the other half of his body would be very pale. It was almost like someone had drawn a line right down the middle of him."

Dr. Kellogg said, I had never seen a case like this before. But happily, as it turned out, other people had and so when they and the librarians were able to make a search of the scientific literature, they found that the condition has a name. It is called Harlequin's syndrome and it has a cure which involves some surgery on the neck, essential surgery.

So in a way it had a good ending.

The newspaper article goes a little bit further and they say correctly that "The program was developed by the National Library of Medicine and that the doctors not only use it to seek information on specific cases, but they also use the service to keep up with developments in their specialties." In other words, it is a part of continuing medical education.

Well, we are pleased with the article. That was just several weeks ago. We know actually that thousands of times a year good outcomes come from using the MEDLINE system.

Another innovation just announced by the library is the creation of a new database, HSTAR, which contains information on health services technology assessment research. Soon NLM will be making available over the same network the full text of all the clinical practice guidelines that are issued by the Agency for Health Care Policy and Research.

I should remind you that the holdings of the library itself still constitute the essential backup resource for the entire National Network of Libraries of Medicine. These 4,000 libraries provide day-to-day reference and lending services to health professionals and they call on the NLM only when they don't have a holding themselves.

Looking briefly at research and development, NLM's funding of its programs: in information science and informatics has been maintained at a level roughly equivalent to previous years. Our increases in funding have been associated with the country's multiagency high performance computing and communications initiative, HPCC.

This HPCC program initiative is an important part of the U.S. science agenda. It has consequently also become an important part of NLM's program in both research and outreach.

NLM has just funded the first 12 HPCC health-related applications. These include test-bed networks, citywide, statewide, national; virtual reality experiments; telemedicine, both statewide and discipline-based systems; and information access experiments linking images to patient records.

These projects constitute essentially the beginning of the biomedical component of the national information infrastructure that is described in authorizing legislation just approved by the House.

They are fully compatible in letter and spirit with the legislation the Chairman has introduced to encourage health service in rural areas, H.R. 3249.

We are proud of another accomplishment. NLM's National Center for Biotechnology Information (NCBI) is now responsible for the NIH GenBank DNA Sequence Database. Since NCBI assumed management of the database in September of 1992 it has grown in size by 80 percent and it has been a critical resource for genome research particularly in several recent discoveries such as agents responsible for hereditary colon cancer.

Over the past year some 25,000 users in the biomedical community have conducted more than 3 million searches of the GenBank database using either the network directly or CD–ROMs. So in summary, the library is making its computerized information services available to an ever increasing audience and it is investing in future, even better information services and systems.

The fiscal year 1995 non-AIDS request for the National Library of Medicine is $135.330 million. I would be pleased to try to answer your questions.

[The prepared statement and biography of Dr. Donald Lindberg follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Library of Medicine

Mr. Chairman and members of the Committee: I am pleased to tell you that the National Library of Medicine has recently taken significant steps to open even further its vast holdings to the world. The Library's entire catalog listing of book, serial, and audiovisual holdings is now available over the Internet through a new system known as "NLM Locator." The Library levies no charge for this access.

Simultaneously, the NLM is encouraging U.S. medical institutions to gain access to the Internet. The Internet is the existing widely used high-speed communications network that is a prototype for the "Information Superhighway" of the future. To help ensure that the health professions are taking full advantage of information on the superhighway, the Library offers access grants to medical institutions. This program, offered by NLM in collaboration with the National Science Foundation, has proved to be very popular. It may be seen as a step toward the creation of a nationwide (and, ultimately, worldwide) electronic biomedical community. This work has been made possible because of funding the Congress earmarked for Outreach in the past and also because of new funds earmarked for NLM participation in the High Performance Computing and Communications (HPCC) initiative.

This committee has heard in the past about how the Library has extended access to its electronic databases to individuals--to doctors, scientists, other health professionals, and students. This emphasis on access for the individual continues. The community of enthusiastic database searchers supported by the Library, reported last year as 60,000, has risen to 82,000. Most of these are individuals who use the Library's Grateful Med software on a personal computer and thus have 24-hour access to MEDLINE and other NLM databases. In addition, of course, the 4,100 U.S. medical libraries are all institutional users of the same services, each handling the information needs of hundreds of physician and scientist users.

It is a pleasure to report that in 1994 the Library took a much-applauded step by opening up its four AIDS-related databases to all users on a completely cost-free basis. Along with this step, we are encouraging access by those who have not traditionally used our databases--patients and the general public. For example, a public library or a community-based health organization can receive a special code from NLM that will allow free access to the AIDS databases. This means that the library or organization can make a terminal available for unlimited searching by the general public. The databases covered include the extensive published literature on

AIDS (journal articles, books, audiovisuals, meeting reports), and also the drugs being tested and clinical trials being conducted. This last includes a listing of clinical trials that are recruiting patients, complete with telephone numbers and other data to help a person or family member to get enrollment information. Another database lists the many organizations that provide information to the public about AIDS.

This opening up of the Library's databases to the public is a departure from past practice. Although the NLM never refused access to anyone, the emphasis was on outreach to health professionals and to the institutions that serve them. We hope to learn about how to serve the public more directly. Will many individuals take advantage of the free access? Will we do a good job? Will we do a good job with underserved populations? Last year some 6 million searches were done nationwide, almost solely by health and medical library professionals. It is estimated that an additional 15 million searches are done each year by those who use NLM databases on compact disk, or who use MEDLINE on commercial online database services, or who use NLM databases through the facilities of our partner organizations in 18 foreign countries.

Another innovation just announced by the Library is the creation of a database, "HSTAR," containing much information on subjects touching on health care reform. "HSTAR," which stands for Health Services Technology Assessment Research, is a database with 1.3 million records. HSTAR is unusual among NLM databases in that it contains references to government reports, books, book chapters, meeting abstracts, and, soon, newspaper articles, in addition to the selected pertinent references and abstracts from MEDLINE and several other NLM databases. The database was developed by the NLM in cooperation with the Agency for Health Care Policy and Research as part of the Library's recent mandate from the Congress to expand its information services in such areas as health services research methods, technology assessment, clinical practice guidelines, bioethical considerations, financing, evaluation, planning, and quality assurance. The emphasis is on the practical: "I can go elsewhere for theory, but I use HSTAR to gain expertise in practical applications such as state HMO plans..." one HSTAR user told us. The database even contains comparison data of various medical equipment and devices on the market--of great value to hospitals in keeping costs down while maintaining quality. The new database should be helpful to administrators, planners, policy makers, legislators, third-party payers, health service researchers, and the information specialists who serve these groups. HSTAR is available under the same conditions as MEDLINE and most of the other NLM databases, that is, at an average cost of about $1.25 per search.

Research and Development

The multi-agency High Performance Computing and Communications (HPCC) initiative, a keystone of the American science and technology enterprise in the 1990s, has become an important part of the Library's program in both Research and Outreach. The Library components that are most affected initially are the Lister Hill

National Center for Biomedical Communications and the National Center for Biotechnology Information. Increasingly, though, the National Network of Libraries of Medicine and the Library's Information Center on Health Services Research and Health Care Technology are becoming involved in electronic highway programs. The National Coordination Office for HPCC, headed by the NLM director, continues to reside at the Library.

A $4.15-million contract, awarded at the end of FY 1993, is supporting a consortium of West Virginia institutions to install a system that applies advanced networking technologies to delivering health care in both rural and urban areas of the state. The objective is to demonstrate that physicians can treat patients using electronic patient records and information from distributed sites, and that a network of primary care and specialized care providers can collaborate to meet community health needs.

In addition to the West Virginia project and the program of grant support to assist medical institutions to link up to the Internet, mentioned earlier, the NLM has just announced that it is funding 11 additional HPCC health-related applications that were submitted in response to our Broad Agency Announcement. They range from testbed networks (citywide, statewide, and national), to virtual reality experiments, to telemedicine (both statewide and discipline-based systems), to information access (linking images to patient records). The successful outcome of these projects will, we hope, help to contain health care costs through sharing scarce resources while raising the quality of patient care.

Another project in the HPCC arena is in the area of imaging. This is the "Visible Human" project that seeks to build an immense digital image library representing submillimeter x-y-z numerical coordinates of the male and female human body. The first phase, to acquire image data from photographic, computed tomography, and magnetic resonance imaging, is now under way, and the set of images resulting will be made available widely to the medical community over the Internet, probably later in 1994. This project promises to provide an unprecedented image resource for use in medical education and in developing computer graphics tools for computer-aided surgical planning.

NLM's National Center for Biotechnology Information in 1992 took over responsibility for the GenBank DNA Sequence Database. The Center has been successful in expanding the scope of the database and the forms in which it is available. Some 3 million searches a year are now being done on GenBank--both online and on compact disk. The Center's scientists also perform research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules and compounds. These methods are widely published and made available to scientists around the world. In summary, the National Library of Medicine is making its computerized information services available to an ever-widening audience, we are creating and making available new databases that respond to national needs, and by supporting High Performance

Computing and Communications projects--both within the NLM and in the medical community at large, we are investing in future information systems and services. I would emphasize that we are doing all this while protecting the integrity of the Library's unparalleled collections, maintaining NLM's basic services to the medical library community, and serving on-site patrons at our facility in Bethesda.

Mr. Chairman, the FY 1995 non-AIDS request for the National Library of Medicine is $135,330,000. I shall be pleased to answer any questions you may have.

Brief Biography

DONALD A.B. LINDBERG, M.D.

Donald Allan Bror Lindberg was born (September 21, 1933) and raised in New York City. He is married and the father of three sons.

He was graduated from Amherst College in 1954 with a degree (magna cum laude) in biology and accepted to the Columbia University College of Physicians and Surgeons. He earned his doctor of medicine four years later from that institution. He is the recipient of Sc.D. degrees (hon. caus.) from Amherst College and from the State University of New York Health Science Center at Syracuse, and an LL.D. (hon. caus) from the University of Missouri (Columbia). Among his academic honors are Phi Beta Kappa, Simpson Fellow of Amherst College, and Markle Scholar in Academic Medicine (1964-69).

After earning his M.D., Dr. Lindberg was an intern and later assistant resident in pathology at Columbia-Presbyterian Medical Center, an Assistant in Pathology at the Columbia University College of Physicians, and a resident physician in pathology at the University of Missouri School of Medicine. This last was the first in a series of positions of increasing responsibility at the University of Missouri: Director of the Diagnostic Microbiology Laboratory (1960-63), Instructor, Assistant, Professor, Associate Professor, and Professor of Pathology (1962-84), Director of the Missouri Regional Automated Electrocardiography System (1967-69), Director of the Medical Center Computer Program (1962-70), Director of the Regional Medical Program Information Systems (1967-70), Professor and Chairman, Department of Information Science, School of Library and Information Science (1969-71), Consultant for Health Sciences to the Vice President for Academic Affairs (1972-73), Director of the Health Services Research Center, and Director of the Information Science Group, School of Medicine (1971-84). In 1984, Dr. Lindberg was appointed Director of the National Library of Medicine. In 1988 he was appointed Adjunct Professor of Pathology at the University of Maryland School of Medicine and, in 1992, Clinical Professor of Pathology at the University of Virginia. In 1992, he was also appointed the first director of the National Coordination Office for High Performance Computing and Communications, a position concurrent with his directorship of the NLM.

Dr. Lindberg is a member of many professional organizations, among them: Sigma Xi; American Society of Clinical Pathologists; College of American Pathologists; American Association for the Advancement of Science; Association for Computing Machinery; American College of Medical Informatics (Board of Directors); Symposium on Computer Applications in Medical Care (Board of Directors); National Board of Medical Examiners (Board Member); National Academy of Practice in Medicine (Distinguished Practitioner); National Academy of Sciences--Computer Science and Engineering Board; Institute of Medicine--Board on Health Sciences Policy. He was a founding member and first President of the American Medical Informatics Association.

He is the author of four books and more than 150 articles, reports, and monograph chapters. In addition, he has served as editor of *Information Methods in Medicine*, *Lecture Notes in Medical Informatics*, and the *Journal of Medical Systems*.

OPENING STATEMENT

Dr. **COLLINS**. Mr. Chairman, 500 years ago Christopher Columbus, after a successful encounter with the Queen Isabella appropriations subcommittee, set sail across the Atlantic and encountered a new world. In the 1960s, an ambitious U.S. adventure, culminated in the landing of a man on the moon. Both these events dramatically altered our view of the world.

GENETICS—A NEW WORLD

Three-and-a-half years ago the Human Genome Project was launched, in no small part because of the visionary efforts of the Members of this Committee. Many historians believe this Project will almost certainly end up on this very short list of major discoveries by humankind. This time, however, it is an adventure into ourselves, to read our own genetic blueprint. This 15-year effort aims to locate and sequence all of the approximately 100,000 genes that define the human organism.

The Human Genome Project will provide: a profound effect on the practice of medicine and a reduction of human suffering; the potential to reduce spiraling health care costs by focusing on prevention; and a much needed shot in the arm for American economic competitiveness through stimulation of biotechnology. Thus, this project represents a remarkable value for the investment, which in the proposed budget for fiscal year 1995 amounts to only 1.3 percent of the NIH total.

Furthermore, the fruits of the Human Genome Project benefit science and medicine and the public almost immediately. A recent issue of Time magazine, which you have in front of you, talks about "Genetics: The Future is Now." A great deal of the information in this article is focused on the Human Genome Project. I encourage you to read the many personal stories as well as how the project is having an impact on medicine.

HEREDITARY FACTORS IN CANCER

Tomorrow here in Washington, there is a workshop on hereditary factors in breast, ovarian, and colon cancer. In the morning session, to kick off this particular workshop, there will be talks given, not by scientists, but by patients. Two of these speakers will be members of a family that is riddled with breast and ovarian cancer at an early age. They are part of a study I was involved in at the University of Michigan.

One member will tell of her eleventh hour DNA test that spared her from unnecessary prophylactic mastectomy. The other will tell how a DNA test warned her of a cancer already present. A cancer which she didn't know she had but discovered in time to allow preventive measures to be taken and probably a cure of that particular tumor.

Nearly every disease except trauma has a genetic component. The Human Genome Project will eventually allow the uncovering of the genetic basis of virtually every condition.

As the Human Genome Project proceeds, more and more similar stories will emerge. Probably everybody in this room can think of something that runs in their family, that tends to afflict their relatives more often than other people.

If it were possible to know your own individualized risks, would you want to? I suspect the answer would depend a lot on whether there were options to be offered. If it was a condition where your risks of dying of that disease or suffering from that disease were reduced by altering your lifestyle, by medical surveillance, or by taking advantage of some new treatment, then I suspect you would be very interested. In fact, that is the essence of preventive medicine.

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS

As we experience these advances in knowledge, however, the potential for misuse of this information also exists. That is why the Human Genome Project has from its outset devoted a percentage of its budget to investigating the ethical, legal, and social implications (ELSI) of this research.

The ELSI program now supports a vigorous research agenda, trying to uncover all the possible consequences of this research, and preparing for the time when DNA testing becomes widespread.

The ELSI program increasingly has turned its attention towards not just research, but policy option development as an outgrowth of that research. These options will aid lawmakers in preventing genetic discrimination, which I think we all agree is something we have to attend to.

As an example of this, you have in front of you a book produced by The Task Force on Genetic Information and Insurance, clearly an arena of much concern. I'm sure most of us would agree an individual should not lose their health insurance because he or she is found to be at risk for some future genetic disorder. Yet at the present time there are no safeguards to prevent that. A major initiative for the ELSI program is to put such safeguards in place.

PROGRESS TOWARD GOALS

How are we doing with progress toward goals with the extramural scientific program? The Human Genome Project funds a large number of centers and investigators all over the country, and I am happy to say that three-and-a-half years into this project, it is both under budget and ahead of schedule. So much so, that our first five-year plan, originally to go through the end of 1995, was scrapped last year because it was out of date. Instead we developed a more ambitious and far-reaching five-year plan that was published last fall in the pages of Science magazine.

We are quite excited about the new plan. It is a stretch. We believe it should be a stretch.

NCHGR INTRAMURAL PROGRAM

The new kid on the block for the National Center of Human Genome Research is an intramural program. The NCHGR extramural effort is devoted to building infrastructure, maps and sequences, and technology to aid us in determining the sequence of the human genome.

The NCHGR intramural program, on the other hand, focuses on the application of genome research to understanding the genetic basis of disease. Establishing an intramural genetics program at NIH was done for a very deliberate reason. The intramural program of the NIH has a long tradition of standing firmly in the interval between basic science and its clinical application, but needed the new genome technological approaches to be completely robust. This is what the NCHGR intramural program will provide.

The NCHGR intramural program has, in its first year of existence, recruited no less than 15 remarkably capable genetic scientists from other institutions around the country. Many of these came from tenured or even endowed positions. Numerous interactions and collaborations have already sprung up between the NCHGR intramural program and other Institutes. I counted about 15 collaborations this morning when I looked over the list.

I would also add that this effort melds nicely with many of the recommendations of the External Advisory Committee, charged with reviewing the NIH intramural program and suggesting ways to invigorate it by bringing in new blood and putting into place very rigorous methods of review.

In summary, Mr. Chairman, the people of this country hope for a better life in the future, free of the ravages of disease that currently haunt us, most of which have genetic underpinnings. The people have that hope.

Yet, Peter Levi has written, “Hope in every sphere of life is a privilege that attaches to action. No action, no hope.” The Human Genome Project is all about action. In fact, the entire NIH is all about action.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1995 is $152,010,000. I will be happy to answer your questions.

[The prepared statement and biography of Dr. Francis Collins follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Center for Human Genome Research

Mr. Chairman, this is the second time I have testified before this committee as Director of the National Center for Human Genome Research, a dynamic, four-year-old research program that in its short life has made unparalleled contributions to our understanding of human disease. My first year at the helm of this organization has been both challenging and rewarding, and I look forward with tremendous enthusiasm to the many opportunities that lie ahead for the Human Genome Project to make an even greater impact on genetic disease research.

The Human Genome Project has been so fast-paced and successful, NCHGR and the Department of Energy's human genome program have reviewed and extended the first set of 5-year goals established by those agencies in fiscal year 1991. The new set of goals covering years 4 through 8, and published in Science magazine, incorporate new technological developments into the research plan, keeping it ambitious and on the cutting edge.

This past year, the number of disease genes discovered using genome technologies was nearly four times that of the year before. Discovery of one of those genes, for a common form of inherited colon cancer, now makes it potentially possible to identify individuals predisposed to this often lethal cancer. Because colon cancer is often completely curable when it is detected early, this represents a prime example of how a gene discovery can lead directly to life-saving interventions. This gene was isolated within six months of when it was located on chromosome 2; in the past, such work would have taken several years.

Continued improvements in gene mapping technologies are likely to spur even greater increases in the rate of gene discovery in fiscal year 1995 and beyond. Genetic maps consist of markers along the chromosome, which let gene hunters know the area their gene is in. The first 5-year goal for genetic mapping has largely been met, and these maps have already played a central role in the search for disease genes. Under the new set of goals for genetic mapping, researchers will now improve upon those maps by developing markers that give better information and are even easier to use.

Once a gene has been located on a chromosome, the next step is to isolate it. Advances in physical mapping, that is, ordering pieces of DNA cloned from chromosomes, are also accelerating as the research groups set up a few years ago move into full-production mode. NCHGR now supports detailed physical mapping efforts on 10 of the 24 human chromosomes and 1 project to assemble a low-resolution map of the entire genome. Our colleagues at Genethon in Paris, partly supported by NCHGR, have also assembled an initial low-resolution physical map of the human genome. Other physical mapping efforts are expected to produce detailed maps of chromosomes 4, 7, X, and 22 by fiscal year 1995. Maps of chromosomes 3, 5, 12, and 13 will be near completion in 1995.

As success in one area always opens the door to new challenges in other areas, the Human Genome Project is beginning to focus its resources intensively on the next technological hurdle: DNA sequencing. Sequencing is the process of determining the order of the chemical subunits of DNA, known as bases. Understanding the order of bases in a DNA molecule is important because the order "spells out" genetic instructions for the cell. Alterations or mutations in the sequence of DNA bases are often the cause of disease. Understanding gene function will require cost-effective sequencing tools that can efficiently examine the anatomy of the various parts of a gene and compare the structures of large regions of DNA between individuals or between humans and model organisms.

Technology development in DNA sequencing has so far focused largely on work in model organisms, such as the bacterium *E. coli* and the roundworm *C. elegans*, because their genomes are small and densely packed with genetic information. A collaboration between NCHGR-supported investigators in St. Louis and a research team in Cambridge, England, has resulted in an important milestone in DNA sequencing: each of these teams has produced 1 million base pairs of DNA sequence from that organism in a single year. The teams plan to increase their sequencing capacity by 5 fold this year. In this aggressive project, researchers are working to maximize state-of-the-art DNA sequencing technology while identifying new areas of development and refinement. NCHGR is also supporting efforts to improve sequencing efficiency by automating several steps in the sequencing process and by investing in radically new technologies for DNA sequencing.

As the maps of the human genome become more complete and more detailed, systematic methods for locating genes and placing them on the maps are needed. One of the goals in the new 5-year plan explicitly addresses this need. We will rigorously support the development of biochemical and computerized methods for identifying DNA regions that encode proteins. Rather than using current gene-by-gene approaches to identifying genes, these new methods should make it possible to identify all the genes in large regions of DNA. Such a large-scale gene-finding technique, known as "exon trapping," finally captured the renegade Huntington's disease gene last year by determining which of the DNA regions on chromosome 4 contained genes and which ones did not. Further research is needed to automate these techniques and make them more efficient for even larger regions of DNA.

The pace of successes in genome research makes it now more imperative than ever that we aggressively develop policy options for the ethical use of these technologies both within and outside the medical setting. Problems of how best to use the medical spin-offs of genome research are becoming more acute as genes for common illnesses are discovered. The gene for hereditary non-polyposis colon cancer discovered a few months ago, for example, is carried by an estimated 1 in 200 Americans. A test to identify individuals predisposed to this illness is imminent. Despite the potential of this test for saving countless lives, neither health care professionals nor the public is prepared to use or understand the implications of the test. The imminent discovery of a gene for hereditary breast cancer will add another example to this conundrum. In view of this situation, the National Advisory Council for Human Genome Research published a statement in the Journal of the American Medical Association recommending that genetic testing for predisposition to certain cancers be delayed until we gain more knowledge about how to deliver these tests in a way that will ensure the best health outcome and that is socially and psychologically responsible. NCHGR's Ethical, Legal, and Social Implications (ELSI) Branch has launched a new study that will give us important information to guide us in making policy recommendations about these issues.

The ELSI branch has already contributed a number of important documents to policy discussion. The NIH-DOE Task Force on Genetic Information and Insurance has examined the issues surrounding health insurance coverage for individuals and families with genetic health risks. The task force has made recommendations about how genetic information should be handled in a universal coverage system and has forwarded those recommendations to the White House Task Force on Health Care Reform. The ELSI branch also funded a study released last year by the National Academy of Sciences/Institute of Medicine Panel on Assessing Genetic Risks. This report offers recommendations for the regulation of genetic diagnostics laboratories, standards for how genetic services should be delivered, and for policies governing the use of genetic information by public health authorities. In addition, the ELSI program collaborated with the NIH Office of Protection from Research Risks in developing a new set of guidelines to protect the privacy of individuals and their families who volunteer for genetic research.

Finally, the newest NCHGR component, the Division of Intramural Research, is rapidly coming on line as a premiere medical genetics research program. Based at the NIH, with its unique ability to translate basic science into clinical advances, this laboratory will serve as a centerpiece for research in human genetics and molecular medicine throughout the NIH. The intramural division will focus on applications of genome science to the problems of human disease. This includes genetic contributions to cancer development, the development of tools to diagnose susceptibility to genetic disorders, and new strategies for gene therapy. In addition, the division's Medical Genetics Branch will provide a home for a dynamic training program in clinical genetics and genetic counseling.

As genetic technologies make their way into mainstream medicine at an ever increasing pace, the importance of public understanding of these technologies is paramount. In this new age of molecular medicine, many Americans lack the necessary understanding of DNA, genes, mutations, and inheritance to make informed decisions with their doctors about their health care. To ensure that citizens gain the most benefit from the new technologies spinning off from the

Human Genome Project, NCHGR will be increasing its educational efforts to prepare the public to better handle these issues.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1995 is $152,010,000. I will be happy to answer your questions.

FRANCIS S. COLLINS, M.D., PH.D

Director, National Center for Human Genome Research

April 14, 1950. Staunton, Virginia

Education:

University of Virginia, 1970 - B.S. (with Highest Honors); Yale University, 1972 - M.S.; Yale University, 1974 - Ph.D.; University of North Carolina School of Medicine, 1977 - M.D. (with Honors)

Professional History:

1976-1977, Fellow in Genetics and Biochemistry, University of North Carolina School of Medicine, Chapel Hill, North Carolina. 1977-1978, Intern in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1978-1980, Assistant Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1980-1981, Chief Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina. 1981-1984, Fellow in Human Genetics and Pediatrics, Yale University School of Medicine, New Haven, Connecticut. 1984-1988, Assistant Professor of Internal Medicine and Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan. 1987-1988, Assistant Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1987-1991, Chief, Division of Medical Genetics, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan. 1988-1991, Associate Professor of Internal Medicine and Human Genetics, University of Michigan School of Medicine, Ann Arbor, Michigan. 1988-1991, Associate Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1991-1993, Professor of Internal Medicine and Human Genetics, University of Michigan School of Medicine, Ann Arbor, Michigan. 1991-1993, Investigator, Howard Hughes Medical Institute, Ann Arbor, Michigan. 1993 to present, Director, National Center for Human Genome Research, NIH, Bethesda, Maryland.

Board Certification:

Board of Medical Examiners, State of North Carolina, 1977
American Board of Internal Medicine, 1980
Board of Medical Examiners, State of Connecticut, 1981
American Board of Medical Genetics, 1984
Board of Medical Examiners, State of Michigan, 1984

Professional Organizations:

American Association for the Advancement of Science; American Society of Human Genetics, Human Genome Committee, Ad Hoc Committee on Cystic Fibrosis Screening, Board of Directors; American Scientific Affiliation; American Federation for Clinical Research; American Society for Microbiology; American Society of Hematology; American Society for Clinical Investigation; Human Genome Organization (HUGO), Executive Council; Institute of Medicine.

Editorial Boards:

Associate Editor, The American Journal of Human Genetics, 1986-1989. Currently: Associate Editor, Genomics; Associate Editor, Technique; Associate Editor, Genes, Chromosomes, and Cancer; Associate Editor, Somatic Cell and Molecular Genetics; Associate Editor, Human Molecular Genetics.

Awards and Honors:

Dean's Prize for Academic Excellence, 1970; National Science Foundation Graduate Fellowship, 1970-1973; Morehead Foundation Fellow, 1973-1977; Alumni Loyalty Merit Award, 1974; Deborah C. Leary Research Award, 1975; First Prize, Student Research Day, 1975; Riggins Scholarship, 1975; Heusner Pupil Award, 1976; W. Reece Berryhill Scholarship, 1976; Medical Faculty Award, 1976; Isaac Hall Manning Award, 1977; Alpha Omega Alpha, elected Junior year, President of UNC chapter, 1976-1977; Intern of the Year Award, 1978; Henry C. Fordham Senior Resident Award, 1980; Charles E. Culpepper Foundation Fellow, 1983-1984; Cooley's Anemia Foundation Fellow, 1983-1984; Anthony Renda Research Grant, 1984-1985; Hartford Foundation Fellowship, 1985-1987; Jerome Conn Research Award, 1986; Paul di Sant'Agnese Award of the Cystic Fibrosis Foundation, 1989; Honorary Doctor of Science, Emory University, 1990; James A. Shannon Lecturer, Massachusetts General Hospital, 1990; Elizabeth Crosby Teaching Award, 1990; Gairdner Foundation International Award, 1990; Von Recklinghausen Award of the National Neurofibromatosis Foundation, 1990; Michiganian of the Year, The Detroit News, 1990; Lynen Medal of the Miami Bio/Technology Symposium, 1991; Young Investigator Award of the American Federation for Clinical Research, 1991; Honorary Doctor of Humane Letters, Mary Baldwin College, 1991; Doris Tulcin Award for Cystic Fibrosis Research, 1991; Elected to Institute of Medicine, 1991; Distinguished Faculty Achievement Award, University of Michigan, 1991; National Medical Research Award, National Health Council, 1991; Dickson Prize, University of Pittsburgh, 1991; Association of American Physicians, 1992; Honorary Doctor of Science, Yale University, 1992; Honorary Degree of Doctor of Science, The Mount Sinai Medical Center, 1993; Jack Saint Clair Kilby Award, 1993; Member, National Academy of Sciences, 1993.

OPENING STATEMENT

Dr. VAITUKAITIS. Mr. Chairman and Members of the Committee, I am pleased to preview some of the National Center for Research Resources' plans to address the changing infrastructure needs of the biomedical research community. NCRR funds vital technologies and shared resources that undergird both basic and clinical research.

As the pace of science accelerates, we must anticipate the needs of the Nation's biomedical investigators for research infrastructure. Today, I will describe our plans for strengthening four high-priority areas for 1995.

First, we will make our national network of clinical research centers increasingly responsive to promising new areas of science. Over the past few decades, biomedical investigators have learned to successfully transplant bone marrow, kidneys, livers, and hearts using the specialized staff and facilities of this network of clinical research centers.

Now scientists at these centers and other institutions are investigating a sophisticated, ultramicroscopic form of transplantation—gene therapy—that inserts genes to develop new treatments for patients with markedly high cholesterol levels, cystic fibrosis, cancer, and immunologic disorders.

Gene therapy is in its infancy. In the not-too-distant future, it may be used to treat sickle cell anemia, hypertension, and eventually many other major diseases and disabilities of humankind.

But to help gene therapy grow from infancy to its full potential, scientists across the Nation need access to the vectors for gene therapy. So NCRR, along with several other Institutes at NIH, will provide regional gene therapy laboratories that will offer state-of-the-art resources that investigators can use on a shared and cost saving basis.

The needs of groups with special health concerns—minorities, women, children, older people—are addressed in NCRR's portfolio. Investigators at one of our clinical research centers have just reported that slow-release sodium fluoride, administered with calcium, is a safe and effective short-term treatment for postmenopausal osteoporosis. If long-term use proves effective and safe, investigators will have found an effective way to prevent fractures that cause disability, particularly in older women.

NCRR will continue to expand clinical research for underrepresented groups at academic institutions. This initiative will help increase the number of minority investigators, boost minority representation as clinical research participants, and expand research on health problems of underrepresented populations.

NCRR also will emphasize training of minority physicians and dentists to become independent clinical investigators. In addition, NCRR will expand support of biomedical engineering technologies to improve patient care. Those technologies include sensors, physiologic monitoring systems, and "smart" drug delivery systems.

Before research reaches the clinical stage, it almost always is conducted in an animal or other research model, which brings me to the second high-priority area. To support scientists conducting basic and preclinical research, NCRR will expand the range of animal and nonanimal research models of human disease, including models involving simpler life forms.

Diseases for which animal models recently have been discovered or developed include Parkinson's disease, Lyme disease, and a variety of genetic disorders. NCRR-supported investigators recently reported that a dog model has the identical gene mutation as children with the most common form of inherited severe combined immunodeficiency disease. That dog model will be invaluable for developing new gene therapy techniques.

The macaque continues to evolve as an effective model for AIDS-related research. Through NCRR's regional primate research centers, access to that model will be expanded to investigators nationwide in conjunction with our research partners, the other NIH Institutes and centers.

Research is most effectively advanced by a combination of models rather than by concentration on only a few. Thus, in 1995 NCRR will expand its resources for transgenic and other targeted mutant animals. With such precise models, it becomes possible to study specific genes responsible for normal cell function as well as for human disease.

The third area of emphasis includes technologies that enable research. NCRR funds a wide range of these technologies regionally and nationally. For example, in collaboration with the National Science Foundation and other Federal agencies, NCRR supports several high-performance computing resource centers that give investigators cost-effective shared access to some of the most powerful computers in the U.S. High-performance computing has enabled development of powerful molecular graphics to examine the structure of proteins and uncover their function.

To make research technologies even more accessible in the future, NCRR-funded investigators are developing telemicroscopy, a technique that links expensive and scarce instrumentation such as an intermediate-voltage electron microscope over a high-speed communication network to create a distributed laboratory across this country. Only eight such microscopes are available to U.S. biologists.

Our fourth initiative focuses on research infrastructure. We plan to increase funding for shared instrumentation grants for state-of-the-art instruments such as cell sorters, mass spectrometers, and DNA sequencers. We also plan to award grants for construction and modernization of academic research facilities as part of a program to enhance the Nation's scientific research infrastructure.

NCRR's programs are unique and diverse. I will conclude by saying that many people take roads, bridges, and other infrastructure for granted until an act of God—earthquake, mud slide, hurricane—destroys it. Funds spent on infrastructure may not seem as glamorous or as high priority as those spent on specific diseases, but infrastructure funds permanently benefit the institutions to which they are awarded and strengthen biomedical research.

Thank you, Mr. Chairman. I will be pleased to answer any questions you may have.

[The prepared statement and biography of Dr. Judith Vaitukaitus follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Center for Research Resources

Mr. Chairman and members of the Committee, I am pleased to preview some of the National Center for Research Resources' plans to address the changing research resource needs of the biomedical research community. NCRR funds vital technologies and shared resources to undergird both basic and clinical research. As the pace of science accelerates, we must anticipate the needs of the nation's biomedical investigators for research infrastructure.

During the past year, NCRR solicited and received hundreds of recommendations from members of the scientific community. These recommendations are articulated in NCRR's recently completed strategic plan and have inspired some exciting initiatives. Today, I'll describe our plans for strengthening four high-priority areas--clinical research, animal models, high-performance computing, and infrastructure.

First, we will make our national network of clinical research centers increasingly responsive to promising new areas of science and to the country's health care needs. Over the past few decades, biomedical investigators learned to successfully transplant bone marrow, kidneys, livers, and hearts using the specialized staff and facilities of this network of general clinical research centers. Now scientists at these centers and other institutions are investigating a sophisticated, ultra-microscopic form of transplantation--gene therapy--that inserts human genes to develop new treatment for patients with cystic fibrosis, cancer, and immunologic disorders. Gene therapy is in its infancy. In the not-too-distant future, it may be used to treat sickle cell anemia, hereditary myopathies, hypertension, and eventually many other major diseases and disabilities of humankind. But to help gene therapy grow from infancy to its full potential, scientists across the nation need access to the vectors for gene therapy. So NCRR, along with several other institutes at NIH, is negotiating to provide regional gene therapy laboratories that will offer state-of-the-art resources that researchers can use on a shared and cost-saving basis.

The needs of groups with special health concerns--minorities, women, children--are addressed in GCRC portfolios, as well as the health problems of an aging population. Investigators at one of our clinical research centers have just reported that slow-release sodium fluoride, administered with calcium citrate, is a safe and effective short-term treatment for postmenopausal osteoporosis. If long-term use proves effective and safe, we may have found a new means to prevent fractures that cause disability, loss of function, and increased risk of death, particularly in older women.

Before research reaches the clinical stage, it almost always is conducted in an animal or other research model, which brings me to the second high-priority area. To support researchers conducting basic and pre-clinical research, NCRR will expand the range of animal and non-animal research models of human disease, especially models involving simpler life forms. Diseases for which animal models recently have been discovered or developed include Parkinson's disease, Lyme disease, and a variety of genetic disorders. NCRR-supported investigators recently reported that a dog model has the identical gene mutation as children with the most common form of inherited severe combined immunodeficiency disease. The animal model will be invaluable for developing new gene therapy techniques.

The pig-tailed macaque continues to evolve as an effective model for HIV-1 and HIV-2 studies. Pig-tailed macaques infected with HIV-2 decrease their CD-4 counts and develop symptoms just as people do. That animal model will be invaluable for developing vaccines and therapies for human AIDS.

Whether investigating AIDS or Alzheimer's, investigators need a wide range of research tools from which to choose. Research is most effectively advanced by a combination of models rather than by concentration on only a few. Thus, in 1995 NCRR will expand its resources for transgenic and targeted mutant animals. With such precise models, it becomes possible to study specific genes responsible for normal cell function as well as for human disease. NCRR is now encouraging the development of "high connectivity" models about which a large body of knowledge is already available and applicable to other systems. Hydras, lobster hearts, and clams, for example, provide insight for diagnosing and treating human cancers and birth defects, cardiomyopathies associated with Marfan's syndrome, and the effects of herbicides. And we support the development of marine models, including fish, abalone and sea urchins, that are useful models for the study of normal development from a few cells to the mature form.

The third area of emphasis in 1995 is to bring the benefits of high performance computing and communications to investigators. In collaboration with the National Science Foundation and other agencies, NCRR supports several high-performance computing resource centers that give investigators cost-effective access to some of the most powerful computers in the U. S. High-performance computing has enabled development of powerful molecular graphics to examine the structure of proteins and uncover their function. Image analysis and the study of biological structures also depend heavily on high-performance computing, as do advanced graphics and biological modeling. An NCRR-supported NMR microscopy resource will allow scientists not only to see anatomic changes in genetically altered mouse embryos through 3-D reconstruction of a "virtual embryo," but also to monitor that viable embryo over time to better understand the impact of genetic modifications.

To make research technologies even more accessible in the future, NCRR-funded investigators are developing a technique known as telemicroscopy, which links expensive and scarce instrumentation such as a high-voltage electron microscope via a high-speed communication network -- to create a distributed laboratory across this country. Only eight such microscopes are available to U.S. biologists. The first long-distance experiment linked a high-voltage electron microscope in San Diego with a computer workstation in Chicago. In the future, we foresee that scientific information highways will link scientists to other sophisticated technologies.

Our fourth initiative will be to create better ways to meet the research and health needs of underserved populations. NCRR will continue to expand clinical research for underrepresented groups at academic institutions. This initiative will help increase minority participation as investigators, boost minority representation in research protocols, and expand research on health problems of minority populations. NCRR also will emphasize training of minority physicians and dentists to become independent clinical investigators. In addition to these clinical, research model, technology, and minority health initiatives, NCRR has many other exciting plans. To mention only a few, we will expand support of biomedical engineering technologies to improve the monitoring of research studies, ultimately to improve patient care. In addition, NCRR will stimulate technological research and development of novel, cost-efficient approaches to disease prevention and medical treatment. These technologies include sensors, physiologic monitoring systems, and "smart" drug delivery systems. We also plan increased funding for shared instrumentation grants which allow 8 to 10 NIH-supported investigators to purchase a state-of-the-art instrument such as a mass spectrometer or DNA sequencer. These vital instruments are too costly for individual scientists to purchase with funds from regular research grants. We also plan to award grants for construction and modernization of academic research facilities as part of a program to enhance the Nation's scientific research infrastructure.

NCRR's programs are unique and diverse. I will conclude by saying that many people take roads, bridges, and other infrastructure for granted until an Act of God--earthquake, mud slide, hurricane--destroys it. Funds spent on infrastructure may not seem as glamorous or as high-priority as that spent on specific diseases. But infrastructure funds permanently benefit the institutions to which they are awarded, strengthen biomedical research, and--most important--improve the health of the American people, for whom all this effort ultimately is intended.

Thank you, Mr. Chairman. The non-AIDS request for the National Center for Research Resources is $286,394,000. I would be pleased to answer any questions you may have.

CURRICULUM VITAE

Judith L. Vaitukaitis, M.D.
Director
National Center for Research Resources
National Institutes of Health

Birth place: Hartford, Connecticut

Education: B.S., Tufts University, 1962; M.D., Boston University School of Medicine, 1966; Internship and Residency, Second (Cornell) Medical Service, Bellevue Hospital, NY, NY, 1966-68; Medical Resident, University Hospital, Boston, MA, 1968-69; Academic Training Fellow, Boston University School of Medicine, 1968-71; Endocrine Section, National Cancer Institute, NIH, Bethesda, MD, 1970; Special PHS Postdoctoral Research Fellow, Reproduction Research Branch, NICHD, NIH, Bethesda, MD, 1971; Senior Staff Fellow, Reproduction Research Branch, NICHD, NIH, Bethesda, MD, 1971-73.

Professional History: March 1993 to present, Director, National Center for Research Resources (NCRR), NIH; 9/92 to 3/93, Acting Director, NCRR, NIH; 6/91 to 3/93, Deputy Director for Extramural Research Resources (ERR), NCRR, NIH; 2/15 to 6/3/90, Acting Deputy Director, ERR, NCRR; 1/15 to 2/15, 1990, Acting Deputy Director, Division of Research Resources (DRR); 6/91 to 11/92, Acting Director, General Clinical Research Centers (GCRC) Program, NCRR; 1986-1991, Associate Director for Clinical Research and Director, GCRC Program, NCRR; 1977-86, Professor of Medicine, Boston University School of Medicine (BUSM); 1980-86, Professor of Physiology, BUSM; 1974-86, Head, Section of Endocrinology and Metabolism, Boston City Hospital, Boston, MA.; 1975-86, Program Director, General Clinical Research Center, BUSM; 1977-80, Associate Professor of Obstetrics and Gynecology, BUSM; 1975-80, Associate Professor of Physiology, BUSM; 1974-77, Associate Professor of Medicine, BUSM; 1974-75, Guest Worker, Reproduction Research Branch (RRB), NICHD, NIH, Bethesda, MD; 1973-74, Senior Investigator, RRB, NICHD, NIH, Bethesda, MD.

Societies and Associations: Association of American Physicians; American Society for Clinical Investigation; American Federation for Clinical Research; The Endocrine Society; Society for the Study of Reproduction.

Honors and Awards: 1987-1989, Associate Editor, Yearbook of Endocrinology; 1984-1986, Editorial Board, Endocrine Research; 1979-84, Editorial Board, Endocrine Research Communications; 1978-87, Editorial Board, Proceedings of the Society for Experimental Biology and Medicine; 1977-1985, Editorial Board, Archives of Andrology; 1973-1980, Editorial Board, Journal of Clinical Endocrinology and Metabolism; 1983, Distinguished Alumna Award, Boston University School of Medicine; 1980, Mallinckrodt Award for Investigative Research, Clinical Radioassay Society; 1983-86, General Clinical Research Centers Committee, DRR; 1979-80, Population Research Committee Study Section, NICHD; 1977-80, Scientific Advisory Committee, Program for Applied Research on Fertility Regulation, Aid to International Development; 1975-78, Breast Cancer Task Force, Epidemiology Subcommittee, National Cancer Institute; Alpha Omega Alpha; Begg (honor) Society.

Publications: Author of over 160 scientific papers with four selected as Citation Classics; editor of one book.

OPENING STATEMENT

Dr. SCHAMBRA. Mr. Chairman, with your permission I will submit my full statement for the record and present a brief oral summary, if I may.

Mr. Chairman, I feel highly privileged to come before you today representing the only Institute or Center of NIH bearing the name of one of your distinguished predecessors as Chairman of this Committee, Congressman John E. Fogarty of Rhode Island. The Fogarty International Center was established to honor the memory of John Fogarty because of a fundamental truth in which he believed passionately: That disease knows no national boundaries and therefore it is in the interest of the American people that this country be engaged in the fight against disease wherever it occurs on the planet.

Mr. Chairman, international cooperation in biomedical research safeguards the health of Americans by tackling diseases before they spread to our shores, by enlisting the scientific talent from researchers from around the world in that effort, and by pooling resources on projects that have grown too complex for any one country to support alone. These benefits may be even more relevant now than they were 25 years ago when the Fogarty Center was established as a focus for the international activities of the NIH.

During the past year we celebrated our silver anniversary and, I am pleased to say, completed a major task: A long-range plan with clear goals for the future. These include the mobilization of international research against the highest priority global health threats; the advancement of new scientific frontiers through international cooperation; the development of human resources to meet global research challenges; and providing leadership in the development of international science policy and research strategies. Our current and future programs reflect these goals.

The Fogarty Center now supports the largest international research and training program in HIV/AIDS in the entire world. This program concentrates on regions of the world with high infection rates, laying the groundwork for future vaccine trials. In fiscal year 1995, the FIC will strengthen these efforts, supporting international AIDS research and searching for ways to prevent new epidemics.

AIDS has emerged due to global demographic changes—and it is neither the first nor will it be the last epidemic to do so. As population pressures increase and human communities encroach on natural ecosystems, new and more virulent diseases are certain to arise. Unsustainable population growth may be the leading global challenge to health, the environment, and economic progress as we approach the next millennium. In response, the Fogarty Center is developing a new international program on human reproduction and population growth to enhance the population research activities of the United States.

Global demographic changes also lead to a decline in the diversity of plants and animals and potential loss of beneficial medicines derived from these species. Thus, the Center supports and coordinates an inter-agency effort, joining American and foreign scientists, indigenous peoples, and the private sector, to address biodiversity conservation and the discoveries and development of new drugs to treat illnesses such as cancer and AIDS.

The FIC has responded quickly to global political changes by supporting research collaboration with scientists in Latin America, Eastern Europe, and Russia and the new republics of the former Soviet Union.

We are now exploring mechanisms for a Middle East initiative to respond to positive political developments which have occurred recently in that region. In fact, Mr. Chairman, even as we speak, there is a meeting going on at the Fogarty International Center of American, Palestinian, Israeli, Egyptian, Jordanian, and other Middle Eastern researchers. Not only are these physicians and scientists developing cooperation on regional health problems, but this initiative by the Fogarty Center has been recognized by the Department of State as an important part of the peace process in that troubled area of the world.

In closing, let me note that as the world grows ever smaller our need to promote health and combat disease looms all the larger. NIH is the leader in this effort, but we have many allies—in Europe, in Latin America, in Asia and in Africa.

Today, the world is coming together in ways and at a pace never before seen. In this process, research to improve human health will be one of the great levers of change—advancing science, our national interests, and the cause of peace.

Mr. Chairman, the Fogarty Center's budget request for fiscal year 1995 for our non-AIDS programs is $13,745,000, and in other appropriations for our AIDS programs is $9,357,000.

I would be pleased to answer any questions you may have.

[The prepared statement and biography of Dr. Philip Schambra follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
John E. Fogarty International Center
for Advanced Study in the Health Sciences

Mr. Chairman, it is a pleasure to appear before this Committee to discuss the global role of the Fogarty International Center (FIC). I am especially grateful for the opportunity to remind the Committee Members of our distinctive mission: to improve the health of the people of the United States--and the world--through international cooperation in biomedical research.

More than a generation ago, Congressman John E. Fogarty championed this mission with the words: "let our second American Revolution be a World War against disease." In the years during and following his courageous leadership in the House, a war was waged. Today, smallpox--once the deadliest of scourges--has been consigned to the ash heap of history. A battle is won but the World War goes on, for, as John Fogarty also said, "disease knows no national boundaries."

In this post-Cold War era, even as dramatic political changes have swept the globe, new adversaries have arisen. New diseases have emerged, and some once-vanquished diseases have returned, quietly developing resistance to our most potent drugs. The AIDS pandemic, and recent outbreaks of tuberculosis and cholera are cause for grave concern. Worldwide, population growth and demographic changes have exacerbated these and other health problems.

International collaboration improves the health of Americans by tackling such problems before they spread to our shores, by cross-fertilizing the ideas of researchers from around the world, and by pooling resources on large and complex efforts like genome research. Two recent examples stand out: (1) a gene for colon cancer was discovered through collaboration between a Finnish scientist (who once trained under a Fogarty Fellowship) and his colleagues in the United States; and (2) an Israeli scientist in the FIC's Scholars-in-Residence Program has isolated a gene associated with one form of leukemia.

The benefits of international collaboration were also recognized 25 years ago with the establishment of the FIC to serve a vital national need--as a nexus for the international activities of the National Institutes of Health (NIH). Over the past year the Center celebrated its silver anniversary and, I am pleased to say, completed a major task: the development of a long-range plan that will guide us into the next millennium.

As Dr. Varmus has often noted, it is not a planning document that has value so much as it is the planning process itself. For the Fogarty Center that process has been both constructive and instructive as we faced the challenges and changing needs of the research community and the global laboratory.

From that process has emerged a clear set of goals. Our first priority must be the mobilization of international research against global health threats. To meet those challenges, we must work to advance science through international cooperation and to develop human resources for the future. The planning process also has allowed us to make strategic decisions in times of budget constraint. Let me now describe some of our programs.

AIDS tops the list of global health threats of concern to the Fogarty Center which supports the world's largest global research and training program in HIV/AIDS. This program develops human resources in regions of the world with high infection rates, laying hopeful groundwork for future vaccine trials. In 1993, roughly 17 percent of NIH AIDS publications were authored or coauthored by an FIC-supported scientist in this program.

Genetic variability of the AIDS virus, and geographic differences in the features of the AIDS epidemic, make such an international approach essential. For example, a clinical trial in Haiti, where infection rates are high, has shown that the antibiotic isoniazid can decrease the incidence of tuberculosis and delay the onset of AIDS. These results have implications for HIV-infected individuals everywhere, including here in the United States where 5 to 10 percent of infected individuals may develop active tuberculosis within one year of diagnosis.

In FY 1995, the FIC is planning to expand its AIDS research activities, strengthening these efforts through additional mechanisms including the new AIDS International Research Collaboration Award. This award will support top-caliber AIDS-related research collaborations between American and foreign scientists, including research on opportunistic infections, emerging and re-emerging pathogens, and diseases linked to factors known or suspected to be related to the spread of HIV.

Pathogenic microbes have always been major participants in human history--HIV is not the first nor will it be the last global epidemic. Historical epidemics such as Europe's black death, or tuberculosis and polio in modern times, have always been associated with changes in human behavior and migration. As the global population increases and urban population densities grow, and as human communities encroach on unfamiliar ecosystems, new and more virulent diseases are certain to emerge.

Thus, the FIC is developing a new program on Human Reproduction and Population Growth to enhance the population research activities of the United States. This program will promote international partnerships between U.S. and foreign scientists and institutions, building on existing efforts and adding an international dimension to ongoing domestic research. It will emphasize research collaboration with, and the training of, foreign scientists from developing nations to study and find solutions appropriate for their own regional concerns.

Global demographic changes also lead to a decline in the diversity of plants and animals, and a potential loss of beneficial medicines derived from these species. The FIC now supports and coordinates an International Biodiversity Program, joining U.S. and foreign scientists, indigenous peoples, and the private sector, to address biodiversity conservation and the discovery and development of new drugs to treat illnesses such as cancer, infectious disease, and mental disorders. Support is shared between the NIH, the Agency for International Development, and the National Science Foundation, pooling resources and programmatic expertise across the Federal Government to address cross-cutting scientific challenges.

Advancing science through international cooperation, and developing human resources are important goals for the Fogarty Center. The Center's prestigious Scholars-in-Residence Program and fellowships for the exchange of American and foreign scientists are significant components of this effort. In FY 1995, FIC fellowships will emphasize new opportunities for young Americans to conduct research overseas, and the needs of scientists from less developed countries. In addition, with support from the NIH Office for Research on Minority Health, we have established an innovative new program to support minority students and faculty members in international biomedical research.

The FIC has responded quickly to global political changes. We now support an award program open to research collaboration with Latin America, sub-Saharan Africa, Central and Eastern Europe, and the new republics of the former Soviet Union. Scientists from the United States and the Czech Republic, for example, are studying mechanisms of viral assembly--important for designing the next generation of anti-viral drugs. The FIC is now exploring mechanisms for a new Middle-East Research and Training Initiative to respond to positive political changes in that region.

In closing, let me note that as the world grows ever smaller our need to understand health and combat disease looms all the larger. The NIH remains a leader in this effort, but we have many allies--in Europe, in Latin America, in Asia and Africa. Today, the world is coming together in ways and at a pace never before seen; in this process, research to improve human health will be one of the great levers of change--advancing science, our national interests, and the cause of peace.

Thank you Mr. Chairman, the FIC budget request for FY 1995 is $13,745,000. I will be pleased to answer any questions you may have.

CURRICULUM VITAE

Name:	SCHAMBRA, DR. PHILIP E.
Date & Place of Birth:	November 8, 1934. Saginaw, Michigan

EDUCATION:

1956	B.A., Rice University
1961	Ph.D., Yale University
1961-1963	Postdoctoral, Institut für Strahlenbiologie, Karlsruhe, Germany
1964-1966	Postdoctoral, University of California, Berkeley

Professional History:

1956-1958	Research Assistant, Biophysics Department, Yale University.
1958-1961	Predoctoral Fellow, National Cancer Institute, Biophysics Department, Yale University.
1961-1963	Research Associate, Institut für Strahlenbiologie, Karlsruhe, Germany.
9/64-2/65	Instructor, Department of Medical Physics, University of California, Berkeley.
1964-1967	Research Biophysicist, University of California, Berkeley. NASA Research Fellowship.
1966	Laboratory Director, National Science Foundation Summer Institute in Radiobiology, University of California, Berkeley.
1967-1968	Grants Associate, National Institutes of Health.
1968-1971	Budget Examiner, Office of Management and Budget, Executive Office of the President.
1971-1974	Staff Member, Council on Environmental Quality, Executive Office of the President.
1974-1980	Associate Director for Interagency Programs, National Institute of Environmental Health Sciences, NIH.
1980-1984	Chief, International Coordination and Liaison Branch, Fogarty International Center, NIH.
1984-1988	Science Attache and PHS International Health Representative, U.S. Embassy, New Delhi, India.
1988-Present	Director, Fogarty International Center, National Institutes of Health.

Honors and Awards:

1984	NIH Merit Award
1989	PHS Superior Service Award
1982-1993	Outstanding Performance Ratings

NEED FOR MEDICAL LIBRARIES

Mr. SMITH. Dr. Varmus, one of my colleagues, Representative Thornton from Arkansas, a former university president knows a lot about science, a lot more than I do. He has a question I am going to put in the record and ask you to answer it about one of the programs.

This library, are we getting to the place where we don't need but one library in the United States?

Dr. LINDBERG. I don't believe so, sir. We actually operate with quite a different philosophy. We receive visits at least once a week, from overseas visitors who are essentially looking for the secret; why do American biomedical practitioners and scientists have such good information services?

And the answer really is outside our walls. It is in the national network of libraries of medicine, some 4,000 in number, with 130 or so resource libraries and eight regional libraries. Only the latter are partially supported by NLM and the secret, really, is sharing.

The computers in our schemes really help persons and institutions that wish to share resources to do so. That is the American secret.

Mr. SMITH. Well, theoretically if you had all the information and everybody had a computer they could just get it from you no matter where they were?

Dr. LINDBERG. In some theory that might be the case, but actually no library is sufficient in itself. I mean, its strength is in its connections with others and knowing where information is. We are the biggest biomedical library in the world but we don't have everything, to answer the question.

Mr. SMITH. How many regional libraries are there?

Dr. LINDBERG. There are eight in the U.S.

Mr. SMITH. Do they cover all regions?

Dr. LINDBERG. They cover all regions, yes, sir.

Mr. SMITH. Everyone is covered by a regional library?

Dr. LINDBERG. Yes. They do a very good job.

But as I said, we couldn't make them do it and we don't even pay very much for them to do it, but we help them to share because they want to share.

Mr. SMITH. What region is Iowa in and where is the regional library?

Dr. LINDBERG. It would be at the University of Chicago.

Mr. SMITH. Who is responsible for keeping up the regional library?

Dr. LINDBERG. Well, NLM, I suppose, is responsible. We really got the authority and the responsibility in 1965 in the Medical Library Assistance Act, which, as you probably remember, follows from the Heart, Cancer and Stroke Report to Congress, and Lyndon Johnson as well.

Funding the regional medical libraries uses the mechanism of competitive contracts, which are recompeted every five years. Then, of course, we meet with the library directors, and each of them have a regional advisory committee which includes physicians and other health care practitioners.

Mr. SMITH. Do you put the same information in each of these eight regional libraries?

Dr. LINDBERG. No. I think it is the reverse philosophy, sir. Each of them has its own strength. I mean, in 1965 I think everyone was aware there were increasing numbers of new medical schools planned. There was a kind of what was viewed at the time as an information explosion and something had to be done to cover all this.

So we drew and I think my predecessors drew upon the strengths as they existed. The great universities had great libraries. They had complementary holdings, so to speak. These computer systems allow a joint intelligence to know where information is, know where books are, and to facilitate the borrowing.

Right at the moment a lot of libraries are canceling journal subscriptions because the prices have gone up 27 percent in the last year, so they will become more dependent on us. That is not something we want.

We take pride that some 82 percent of the nation's medical library loan requests are being filled locally. We should be drawn upon as a court of last appeal, so to speak, but increasingly we are being drawn on as the prices increase.

Mr. SMITH. Why does a medical school need a library of their own if they can plug into these regional libraries?

Dr. LINDBERG. I think it will be true even in the foreseeable future, Mr. Smith. But in most cases what we are provided by this MEDLINE search is really a citation and abstract—one page out of a 10 or 20 page article. It isn't really all of the article. You would have to get that by fax.

Mr. SMITH. Now, are you telling me that all medical schools then need a library of their own, a substantial library?

Dr. LINDBERG. For the most part, yes. Several times I have had to choose between a library and a librarian. I have always chosen the librarians because they are able to be the experts to help us all know where information is and how to get it, how to use the networks, how to use the borrowing mechanism, and how to use the entire system. I think, if for no other reason than that, all the medical schools would certainly want it.

COST OF MEDICAL LIBRARIES

Mr. SMITH. How much a year does it cost to keep a library up, for a good medical school?

Dr. LINDBERG. A couple of hundred thousand dollars, at a minimum. But the average cost would be about $1.7 million.

Mr. SMITH. That would surely be a minimum.

Dr. LINDBERG. Yes, you asked at a minimum.

Mr. SMITH. Law offices spend $20,000 just for a library in a law office.

Dr. LINDBERG. It is possible to spend $20,000 for a single journal subscription. It is getting horrible.

I just participated in dedicating the new medical library at the Vanderbilt University. It has cost them $20 million, of which $10-and-a-half was from a private donor, who was a physician graduate of their school.

They emphasized, I must say, that a library is a place as well as an idea. It is in the center of the campus. It is a quiet, contemplative place with extensive resources and very knowledgeable people. It helps patrons get beyond that library to that national network to Internet.

Mr. SMITH. Well, then, is there a basic investment that needs to be made, in terms of several million dollars at the beginning, and then you have an annual upkeep?

Dr. LINDBERG. Unquestionably, yes. But if you reduce it all down finally to what each individual query costs, it is very, very small. A query such as the one I described about the Harlequin's syndrome involves just the costs for searching a database, about $1 to $1.25. They are trivial. Patients pay more than that for parking when they go to see a doctor at an outpatient clinic.

So it does add up to millions and, in our case it adds up to $100 million, but the unit cost and the gain from a correct diagnosis is so great that I think I have to say that we are a bargain. Of course, you are surrounded by bargains probably.

Mr. SMITH. I have some other questions but I will wait for Mr. Porter.

BIODIVERSITY INITIATIVE

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Schambra, you mentioned your biodiversity initiative at some point in your opening statement. I think it is one of the most exciting things that you are doing. Can you give us a little more detail on how the funds were spent and are there additional ways to reach the objectives of the program?

Are there funds in your request to pursue these ideas, and if not, how much additional funding could be used for these purposes?

Dr. SCHAMBRA. Mr. Porter, yes. We are very pleased with the way our initiative in biodiversity has developed. As you know, this is a multi-agency and inter-agency effort involving not just several Institutes of the National Institutes of Health but the National Science Foundation and the U.S. Agency for International Development as well.

In the first year of this program, fiscal year 1993, we had enough money from the three agencies, excluding the Fogarty International Center at that point, to make three awards.

The first one went to Dr. David Kingston of the Virginia Polytechnic Institute to study rainforest plants in Suriname.

The second award went to Dr. Timmermann at the University of Arizona, who is working with collaborators to study arid land plants in Argentina, Chile, and Mexico.

The third award went to Dr. Meinwald of Cornell University, to study insects and related species from the dry tropical forests in Costa Rica.

You will recall last year this Committee provided the Fogarty Center with additional funds, which allowed us to increase the program and announce two additional awards in fiscal year 1994 for a total of five awards.

Of those two additional awards, Dr. Walter Lewis of Washington University in St. Louis, will study the Andean tropical rainforests of Peru. The final award, to Dr. Brian Schuster at the Walter Reed

Army Institute of Research, will focus on the search for cures of parasitic diseases from rainforest plants of Cameroon and Nigeria.

So it is kind of an eclectic and exciting mixture of not only investigators but countries and biodiverse species at this stage.

You asked us about other opportunities. What we have come to realize, as we have worked with the community of scientists concerned about biodiversity, is that there is a great deal of activity going on. Much of the activity is supported by the National Science Foundation, to identify and collect species of plants and animals, but there is very little being done to explore the potential pharmaceutical value of those collections.

We feel that with some additional resources we would get some time in the future, we might be able to add a biomedical component to the work going on in other agencies. Our thought was that if we could award something like 25 grants at about $40,000 each, we would make a very significant addition to this very fine initiative, for which the Congress has already shown its support for.

HEALTH AND POPULATION INITIATIVE

Mr. PORTER. Can you tell us about your proposed initiative on health and population? It seems to me this is one of the areas where we really ought to focus more of our resources in.

Dr. SCHAMBRA. This is one of the issues that emerged very strongly from our efforts over the past year to develop a long-range plan for the Center and to begin to focus and sharpen our activities on those issues and problems that clearly impact on global health.

As you know, for the past six years we have supported a major program related to HIV infection and AIDS. In fact, it is the world's largest international training and research effort associated with the AIDS pandemic. Based on that experience, and discussions with scientific colleagues in the academic community, we are developing a similar international training and research program for Health and Population. Uncontrolled population growth is clearly an issue that has major impact not only on economic development and the economic progress of people, particularly in the developing parts of the world, but impact on the environment and, in fact, can even be a source of new and emerging diseases that arise, such as the AIDS epidemic.

It is out of that background that we have chosen to pick population as our second major global health issue. We have already had extensive discussions with our colleagues in the National Institute of Child Health and Human Development about developing this particular initiative and hopefully will begin next fiscal year.

NCHGR INTRAMURAL PROGRAM

Mr. PORTER. Thank you, Dr. Schambra.

Dr. Collins, judging from the budget request, the Genome Center is clearly a priority for this administration and one that I support and agree with. I wonder if you could explain the importance of the intramural program and the benefits it brings to NIH generally?

Dr. COLLINS. I appreciate the opportunity to do so.

The NIH intramural program has enormous strengths and has had so for decades in a variety of scientific disciplines which stretch from basic science to clinical trials and almost everything in between.

In the last 10 years, and particularly in the last four or five, there has been a new approach to understanding disease based on something called “positional cloning.” This technique allows you to identify a gene responsible for disease without knowing ahead of time what it is going to look like.

This is a strategy which is enormously powerful because you don’t have to know the answer to start, but it is quite difficult. It requires a lot of genome technology, a lot of labor, and it is the sort of thing which one investigator’s laboratory would have a hard time setting up on their own because of its complexity and the expertise that it requires.

It has been recognized for four years that the intramural program at NIH would greatly benefit from having access to these genome technologies. In fact, a plan for an NCHGR intramural program was drafted about three-and-a-half years ago by Dr. James Watson, my predecessor.

The purpose of this intramural program should be to bring together a hub of investigators with expertise in genome technologies and in the application of those technologies to an understanding of disease, including diagnostics and gene therapy.

And it is the mission of this new NCHGR intramural program to accomplish those goals. I would say we are off to a very good start, given that this effort is a little less than a year old.

Some people have asked, “Why does it have to be the size that it is?”

In this situation there is a real argument to be made for critical mass. It is sort of like a chain. If you have a missing link, you don’t have the strength you need. If you want to find a gene that causes disease, you have a variety of steps that you have to follow, each one of which requires crucial technologies. If you are missing one of those steps, you don’t get to the endpoint.

Furthermore, to recruit really world class scientists, I think you have to put them into an environment with other individuals who have complementary expertise. In fact, a very important part of the successful inauguration of this program has been the ability to recruit quite a number of talented people at once.

If I could take one more minute, I think some people genuinely have trouble understanding the difference between our extramural program, which is devoted to infrastructure—the maps, sequences, and technology—and the intramural program, which is more applied research. I would like to offer the following analogy which perhaps would be helpful.

Imagine that you are trying to build a hospital to practice genetic medicine, a hospital which will have the most powerful approaches available to an understanding and treatment of disease.

If you are going to build such a hospital, you need infrastructure: Bricks, mortar, wires in the walls, a local area network, all of those things and more to make the place hum.

What the extramural Human Genome Project is providing is that infrastructure, that set of tools and materials that everybody needs.

Now, within that hospital you will have many different wards where different expertise is being applied, and all the other Institutes of the NIH are, in fact, doing just that. You have heard constantly in these hearings about the many advances in research that have to do with genes. Those advances, I think, have already benefited by the infrastructure provided by the extramural Human Genome program.

Then, what is the intramural program? It is the main operating room of this genetic medicine hospital. You must have that facility if you are going to be able to do the most difficult, the most risky things. That is what the overall NIH intramural program has always stood for. But, that sophisticated operating room will only succeed if it is supplied with high-tech expertise, instruments, and people trained to use them.

That is what the intramural effort in NCHGR is there to provide, to make that operating room of the intramural program as effective as it needs to be, by bringing into it people who know how to use the gadgets to actually treat and cure disease.

That is why I think it is not appropriate to try to balance the extramural program against the intramural program and say which is more important. It is very hard to make that distinction, they are designed to accomplish different things.

Mr. PORTER. Dr. Collins, can you tell us what significance there is that you ride a motorcycle and Dr. Varmus rides a bicycle, if any?

I thought this article in Time magazine was wonderful in terms of telling people what you are doing and what is happening in genetics and what the role of the genome project is. And there is nothing wrong with popularizing things that ought to be popularized in people's minds. I thought that was very good.

Dr. COLLINS. I think Dr. Varmus has learned to modify his risk taking behavior more effectively than I have.

SHORTFALL IN FUNDING FOR NCHGR

Mr. PORTER. You said in your testimony that the project has achieved most of its original five-year goals ahead of schedule despite the fact that funding has lagged behind the recommendations in the five-year report.

The original 1991 budget plan for the project suggested an extramural budget of $173 million for the project in 1995 but the President's budget proposes only $112 million in that area. What effect will this budget deficit have on your ability to continue the scientific achievements?

Dr. COLLINS. The original budget projections for the extramural Human Genome Project were based on a careful scientific analysis in 1991, applying the estimated inflationary index for biomedical research. That is how the $173 million estimate was calculated for the extramural budget for 1995.

Obviously, that estimate is not what has happened. The escalation of funding for the Human Genome Project has not kept pace with the ramp up that was recommended by the National Academy of Sciences, the Office of Technology Assessment, and other august panels.

We have tried to cope with the shortfall. In fact, maybe we have been so successful that it casts the budget estimates into doubt, because I already indicated that we have achieved success in a number of our milestones. But I need to clarify this.

We put the majority of our investment in the Human Genome Project in its first three-and-a-half years into the building of genetic and physical maps, because that information is so crucial to the community of disease gene hunters and others. We felt that effort had to proceed flat out.

DNA SEQUENCING INVESTMENT

What we have not been able to invest in, Mr. Porter, as a consequence of our budget constraints, has been the development of technologies, particularly for DNA sequencing. Sequencing means reading every single letter of the set of 24 phone books that constitutes the human genome.

We have been making investments in the sequencing area only modestly because of the limitation in the availability of funds. And in a real sense this is beginning to create serious difficulties.

We are moving into the phase where the majority of the Human Genome Project will be focused on sequencing, and we have not been able to push along the development of new technologies at the rate that we would have liked. Therefore we are now beginning to experience some of the consequences of that gap between where we hoped to be and where we are.

I believe that we can close that gap. There are new technological developments that are happening in the sequencing arena that are enormously exciting. Some people argued up until last year that maybe it wasn't yet time to put the investment in sequencing because we didn't quite know what technology to use or develop further.

I think we do know now. Even the most skeptical members of the genome community will now tell you, "I can see how we are going to get this job done." But we have a lot of work left to do.

Unless we figure out some way to close the gap between where we thought we would be and in where we are in DNA sequencing, then we may not be able to achieve the goal of getting the whole Human Genome Project done by the year 2005.

That would be a terrible shame because we know how to do it, and I think we can do it cost-effectively. The advantages of doing it earlier rather than later are obvious in terms of the consequences for medicine. In summary, the Human Genome Project is a relatively modest investment for a very large payoff.

NCHGR SUCCESS RATE

Mr. **PORTER.** If you look at your extramural award rate, it has declined from 28 percent in 1993 to 17 percent in 1994 to 15 percent projected in 1995 under the request.

Is this simply the result of constrained resources in an area of rapidly growing opportunity, or is this in part the result of a strategic decision to concentrate more resources in the intramural program?

Dr. COLLINS. I would argue that the NCHGR intramural program has not taken resources away from the extramural program. I feel quite strongly that that should not be the case.

The NCHGR intramural program had its own rationale for existence. That budget was argued before this Committee as a high priority for the vigor of the entire intramural NIH campus, and for seeing genome applications yield fruit in an understanding of disease as quickly as possible.

So I shall always resist the concept that one program can be traded off against the other program.

It is true that the extramural program has not been able to achieve the funding rate for grant proposals that we would like. The estimated success rates you just quoted indicate that we will come out very near the bottom of the Institute's, centers, and divisions as far as our ability to fund grants. This is potentially quite disheartening. It comes at a time, of course, when there is a lot of enthusiasm about this project and a lot of good investigators coming into the field.

NCHGR FOCUSED GOALS

We are a little different than the other Institutes because we have a set of very focused goals which we must achieve. Many of those goals involve high-intensity, high-throughput, high-efficiency efforts which are best carried out in large centers that can achieve that kind of economy of scale. I think we cannot achieve the goals of the Human Genome Project without both research centers and other large programs. Those are expensive, but I think they are a good investment.

As a consequence of investing in those centers, the funds available for individual investigator-initiated grants is limited, much more so than I wish it were. It is a combination of those trade-offs plus the fact that we have a lot of people interested in genomic research coming into this field that leads to this frighteningly low success rate prediction. I wish we could do something about it.

Mr. PORTER. Thank you very much.

SHARED INSTRUMENTATION GRANT PROGRAM

Dr. Vaitukaitis, I wrote you earlier this year about the Shared Instrumentation Grant (SIG) program, and I appreciated your reply.

As you wrote to me, the President's budget contains an increase for the SIG program from $9 million to $9.5 million. This is well below the $33 million the program had been funded at until 1991.

I would be interested to know what priority you assign to increased funding for the SIG program and how the center determined the funding increase for 1995.

Dr. VAITUKAITIS. We think that funding for the shared instrumentation grant program is very important. In fact, yesterday I spent the entire day with investigators at Yale University discussing the problem and the need for more shared resources to really advance the kind of research you have heard about today, as well as all last week.

During the past year, we have developed a strategic plan for NCRR in concert with the academic community. In discussions with that community, funding for the shared instrumentation grant program has been viewed as a very high priority.

In the development of the budget for fiscal year 1994, and early 1995, we have had to set priorities across all our programs. Two-thirds of our entire budget is focused on shared research resource facilities, biotechnology resources, regional resources for primate research and regional resources for clinical research. Within that context we have to balance what we can do.

We would like to be able to restore the shared instrumentation grant program to its $32 million level, but there is no way we can do that in light of our priorities across our several programs. Our goal is to try to increase funding for SIG at a rate that will fit within the constraints of our budget and the instrumentation investments that we can appropriately make.

CLINICAL RESEARCH CENTERS

Mr. PORTER. Can I next ask you about the general clinical research centers at NCRR? What role do they play in supporting gene therapy?

Dr. VAITUKAITIS. The clinical research centers are playing a central role in the extramural community's effort in gene therapy research. In fact, it is that program that has taken the lead in developing a Request for Applications in collaboration with several other Institutes—the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases along with the National Center for Human Genome Research—to develop vectors for gene therapy to be used by investigators across this country.

We can't afford to put these kinds of expensive resources in every city or in every one of the 74 clinical research centers. We need to do it on a shared basis, again going back to the theme of shared instrumentation.

About one-quarter to one-fifth of all research projects across that network of centers address rare diseases. Rare diseases themselves are very rare, but collectively they are very common, and the clinical research centers play an important role in the transfer of molecular genetics research advances back to patients.

The first somatic gene therapy done in this country was done at a general clinical research center at Dr. Collins' former university, at the University of Michigan.

The clinical research centers program provided the support, the sole support from NIH at that point, for the human applications laboratory at that university to develop the vector for treating the patients with the low density lipid protein for abnormally high cholesterol levels. The CRCs play a critical role for clinical research in molecular therapies and will play an even greater role in gene therapy research in the future.

MEDICAL LIBRARY NETWORKING

Mr. PORTER. Thank you.

Dr. Lindberg, I understand that the NLM recently announced the development of networks to link hospitals, physicians' offices, and medical libraries to improve the exchange of the medical data, and I believe you mentioned this in your opening remarks.

Are many hospitals and offices currently linked to medical libraries and what are the long-term benefits of this type of linkage?

Dr. LINDBERG. We think the long-term benefits are great. Right at the moment, the national network utilizes the alternative commercial systems that are rather slow and rather expensive. The new Internet high-speed highway offers the opportunity to send images as well as ordinary text, to send the full text. Those who retrieve full text probably would have to pay the copyright holder for that. So all of those are big, big improvements.

Another aspect of it is the possibility of telemedicine. That is something we are interested in, the collaborative arrangements for treating a patient at a distance using the networks.

To answer your question, the level of internet use by medical institutions is a little disappointing to me.

The good part is that only 26 percent of university academic medical centers are not attached to the Internet. But the reverse is true for the ordinary hospital. Seventy-five percent, are not attached.

So it is good news for the universities, but we have got a long way to go to get the real health care delivery facilities of the country attached and using this most modern network.

Mr. PORTER. Thank you all very much. Thank you, Mr. Chairman.

RESEARCH EQUIPMENT COSTS

Mr. SMITH. Dr. Varmus, when you make a grant, a part of the money obviously is for equipment, sometimes very expensive equipment, and when that team is done with that equipment what happens to it?

Dr. VARMUS. The equipment belongs to the grantee institution, so it remains with the institution.

Mr. SMITH. Sometimes they don't have a use for it, do they?

Dr. VARMUS. That is possible.

Mr. SMITH. Well, is there any way to keep track of it so that maybe some other grantee could use it?

Dr. VAITUKAITIS. The NCRR supports biotechnology centers that have very expensive equipment, and if we are aware that the grantee is not going to continue on, we will work with the university to have that piece of equipment moved to another university where the investigators have the requisite skills and needs for that equipment, because it is totally inappropriate for that equipment to just sit and collect dust.

This is not a common problem because of the demand for these kinds of equipment. We are certainly in tune with the situation and monitor it very closely.

Mr. SMITH. Well, does the new grantee then buy it from the old grantee?

Dr. VAITUKAITIS. No. It would be transferred to the new grantee institution.

Mr. SMITH. You own the equipment.

Dr. VAITUKAITIS. The bottom line is that we want to make sure that someone is using the equipment and we work with the university officials.

As Dr. Varmus stated, the equipment does belong to the university but they may have no use for it scientifically. They usually work with us and we can transfer that equipment to another institution so it can be used or upgraded, if needed.

Mr. SMITH. Do you keep a record some way in the computer or something about where valuable equipment is located?

Dr. VAITUKAITIS. Within our network of biotechnology centers we know where all that equipment sits. First of all, if we were concerned that a center may be phasing out, we will not provide any updated equipment for that center because it would not be a wise investment.

Mr. SMITH. And if a new grantee gets a grant, are you informed in some way where there might be equipment that they would need?

Dr. VAITUKAITIS. The grantees are the ones that initiate the request.

Equipment may be so expensive that we cannot provide the entire funding; so we advise the potential grantee of that and have them try to find whatever funds we can't provide through their university or private foundations.

Dr. VARMUS. I might say, Mr. Smith, in the current environment, with fairly stringent fiscal control on grants it is very uncommon for a single grantee to be able to obtain funds for an expensive piece of equipment. That grantee who might need the equipment for his research will find it incumbent upon himself or herself either to find a partner for the research or to build a multi-investigator award that would be suitable for some of the kinds of research requests that Dr. Vaitukaitis would award.

Mr. SMITH. When the amount of the award is determined, at that point do you know whether or not they are going to have to acquire new equipment or if they will be able to get equipment from somewhere else?

Dr. VARMUS. In general, a traditional NIH grant request has an equipment budget. However, most of those awards would not be flexible enough to allow a large increase in the purchase of a very expensive piece of equipment. Requests for such purchases would usually be handled through a special grant program sponsored through the National Center for Research Resources (NCRR).

Dr. VAITUKAITIS. A request for that kind of equipment may be in the millions of dollars, and we certainly don't have the level of funds to provide for that kind of equipment.

We will provide incremental funding over a couple of years only with the assurance that sufficient supplementary funding would be available to obtain the level of equipment necessary, so that the investigators can carry out their proposed research at that center.

Mr. SMITH. And that the equipment is not available from some other source.

Dr. VAITUKAITIS. If the funding is not available for the equipment and we can't afford to provide it, then we can't fund the grant.

Mr. SMITH. Dr. Varmus, I asked in several instances, but I wish you would do it for each of the Institutes, to determine to the extent that you can what these resources were devoted to that are represented by the grantees and the applicants that did not get a grant. Do you know what I mean?

Dr. VARMUS. Yes, I do. We discussed it before and we will be looking at this.

Mr. SMITH. So we can kind of find out and get some idea about what happened to them.

[The information follows:]

EFFECT OF LARGE EQUIPMENT COST ON GRANT FUNDING

NIH grantees are rarely denied funding as a result of the high cost of equipment required to perform the scientific activity. When the grant proposal includes equipment costs that are prohibitive, NIH works closely with the grantee to find alternative ways to conduct the proposed research. Information regarding the numbers of grantees that are unable to accept their grant award as a result of lack of funding for expensive equipment is unavailable at this time. However, on an Institute by Institute basis, such instances rarely, if ever, occur. NIH will continue to review instances where this situation may occur and to assist the grantee in exploring alternative methods to gain access to essential equipment to conduct research.

GENETIC AND ENVIRONMENTAL INTERACTIONS

Mr. SMITH. Dr. Collins, we discussed here a few days ago the relationship between sickle cells and malaria.

Dr. COLLINS. Yes.

Mr. SMITH. And that through the selective process over a million years or whatever it may be, people with sickle cells that lived in a malaria-infested area were able to survive in greater numbers than those that didn't have sickle cell, so it was an advantage.

But then when they moved into an area where you don't have malaria, it was a disadvantage because they could get sickle cell anemia. In other words, there is a relationship between malaria and where your ancestors lived or their environment. Are there other diseases where there is this relationship?

Dr. COLLINS. I think you touch on a very important point, Mr. Chairman. The interaction between our genetic predispositions and the environment can determine whether an individual gets a disease or not.

I think the malaria example is a very good one. I spent some time in the Delta area of Nigeria working in a small hospital there. If you tested the residents of that particular area for the presence of the sickle cell gene, you would find about 15 to 20 percent of them are carriers. That is an incredibly high percentage.

But if you are a sickle cell carrier and you get malaria, particularly as a child, you are much less likely to have a fatal case of it. Yet those of us who don't have that trait, who get malaria, as I have had and I gather you have had as well, can certainly testify to the severity of that disease if you have no protection against it.

This is an excellent example of that kind of gene-environment interaction, but there are numerous such examples. In fact, one would say this is almost the rule rather than the exception.

As we are learning, for instance, about diseases that cause cancer, one very interesting example of this interaction between genetics and the environment emerged. There is much excitement right now about being able to identify the one million Americans who are at very high risk for getting colon cancer based on gene discoveries that have happened in the last three or four months. The potential exists to be able to warn those people that they are at high risk and get them into preventive medicine programs in order to catch their tumors while they are still small and curable.

Now if you look at families who have that particular predisposition, you find that 150 years ago in addition to colon cancer they were getting stomach cancer as well. Lots of family members had stomach cancer then and now they are not developing it. In fact the incidence of stomach cancer in general in the Western world has dropped.

Another part of this example is in Japan, where stomach cancer is relatively common. Individuals who have this genetic predisposition in Japan get stomach cancer even more than colon cancer. So here is an example of a gene that has this ability to predispose somebody to getting cancer, but it is clearly something about the environment that determines which kind of cancer they get.

Now the real silver lining in this example is that if there is that much interaction between genetics and the environment maybe we can figure out what environmental protection will keep people from getting the cancer at all. That is a major goal of trying to understand these genetic disorders.

GENETIC EPIDEMIOLOGY

Mr. SMITH. Is there any material in the library or is there any attempt to try to define these environmental relationships to certain diseases and make them available as an alert, maybe, to medical professionals when they are looking for possibilities of disease?

Dr. COLLINS. Yes, I think there is.

The whole field of genetic epidemiology, as it is called, is devoted to understanding the interactions between genes and populations and environments. Part of the problem, though, is that we have not been able to cleanly discern the genetic contribution and divide people up into categories based upon their particular genetic risks. We haven't been able to sort through the very complicated system and, say this is the genetic part and this is the environmental part.

Ironically, our ability to understand genetics may have enormous consequences for our ability to understand the environmental impact because if it is not genetic, it is therefore environmental.

Mr. SMITH. Of course, another problem in the last 300 years, especially the last 100 years, is that people travel all over the world and go from one environment to another environment. This makes it more difficult, but in countries other than the United States especially and in many of the countries, this could be very valuable information.

Dr. COLLINS. Certainly. It is clear from genetic epidemiology studies that genes we now identify as causing diseases in the Western world may in fact have been beneficial in other environments.

Hypertension may be so frequent now in the West because of a need in some cultures to hang on to your salt. High cholesterol may be a problem in our environment because we take in so much fat. But cholesterol is an important substance to hang on to if you need it.

All of these things will become clear, I think, when we can identify the specific genetic basis for each of those conditions.

EDUCATING THE PUBLIC

Mr. SMITH. Well, we find, of course, more and more all the time that discovering new chemicals is not the answer to everything. And the environment of our ancestors has something to do with our susceptibility to certain diseases and risks. As we discussed here during these Institute hearings, life-style has a lot to do with it, too.

So I am coming back to my question about whether or not we are packaging and disseminating the information that the National Institutes of Health has or is capable of providing well enough so that individuals can acquire and use it at will to change their life-style, and so that those who have ancestors that came from certain environments may know that that has something to do with their susceptibility to disease?

This whole question about dissemination of information, is it adequate?

Dr. COLLINS. I think it is an excellent question, Mr. Smith, and I think many of us are coming to grips with the fact that science cannot operate in an ivory tower without taking responsibility for educating the public about the consequences of that effort.

The whole ethical, legal, and social issues component of the Human Genome Project takes as a premise that one of its major areas of interest is the education of the public and health professionals.

Most practicing physicians have had little or no training in genetics in medical school. It is a relatively new field. Medical school curricula do not exactly move swiftly when change is needed, and we are facing the possibility of having a whole cadre of health professionals for whom the area of genetics is unfamiliar. We need to move swiftly to do something about educating these professionals.

You could argue that this issue of Time magazine is a form of dissemination. The kind of media attention given to the Human Genome Project, when it is done well, can be very helpful. Unfortunately, there are times where it is not done so well, and I think it terrifies people.

Mr. SMITH. It seems to me, Dr. Varmus, we have depended in large measure upon the information you have disseminated to individuals through health professionals, but a lot of people don't see a health professional until it is too late.

Dr. VARMUS. Yes, I agree with that. We have made efforts to reach the general public in many ways.

Mr. SMITH. We need to reach the individual so they will reach the health professional earlier.

Dr. VARMUS. Yes.

Mr. SMITH. So that they will change their life-style and never need to see the health professional.

Now, Dr. Alexander, I believe, said you have an education program in his Institute. What is that?

Dr. VARMUS. We have quite a few through the Office of the Director, as well. Most of the Institutes also have educational outreach of various kinds. Some of these outreach programs are directed at grades K through 12, where we try to teach some of the principles of biology and help to encourage young people to adopt a healthy life style.

Mr. SMITH. How do you package and disseminate that information?

Dr. VARMUS. Well, there are a variety of programs. For example, as one of our interests as a scientific agency, NIH is interested in health education to try to attract the best possible students into the study of biology and biomedicine.

Mr. SMITH. Well, how does Dr. Alexander's Institute package and disseminate the information?

Dr. VARMUS. I would have to consult with him about the specifics of his program.

Mr. SMITH. I see.

EDUCATING STUDENTS

Dr. COLLINS. I would be happy to tell you about ours.

Mr. SMITH. How do you do it?

Dr. COLLINS. We feel very passionately that education about genetics is a crucial part of our mission and we have both an intramural and extramural effort in this regard. We estimate that based on these efforts we have reached out and in some way informed over half a million people last year.

Mr. SMITH. How did you do it?

Dr. COLLINS. Through a variety of ways. One is by giving grants to institutions all over the country, including one in the State of Iowa. This Iowa center has one of our most vigorous genetic education units to educate high school biology teachers, which we think is a very powerful way to get the word out so the teachers teach the students and you multiply the outcome.

In the intramural program here at the NIH, I have brought in a new coordinator, a Ph.D. educator from the University of Michigan, and she has put together a very vigorous, ambitious effort to reach out to the Washington community in order to educate high school students and the general public.

We are putting on a number of public outreach programs which are designed for the nonexpert. We have videotapes that we produced which are requested by educators for use in the classroom. We have sent out tens of thousands of these to interested individuals, as well as a series of brochures which we send to community colleges, high school biology teachers, and other requesting parties.

We could do more. I would like to.

I think you put your finger on a very important issue. If the consequences of this explosion in biomedical research which has so many potential benefits are going to come true, we must have an educated public. If they don't know when to ask a health professional for input, then we will have failed in our mission.

Mr. SMITH. Well, and we have television stations now, radio stations, the print media running stories. There must be an interest in it.

Dr. COLLINS. There is.

Dr. VAITUKAITIS. Through our science education partnership award program we have an award with a PBS channel in Pittsburgh. That station has developed a series of programs that is called "The Universe Within." These are separate modules that teach kids not only about science but about healthy life choices. It is geared toward kids as well as adults to make informed decisions.

We also provide support for over three thousand students each summer to work in laboratories to learn about biomedical research and the impact of life styles on their own health. We are hopefully also having an impact on the pipeline for biomedical research in the future.

We are also retooling the science teachers from K to 12 within this program by having them come to work at universities to learn what kinds of science is going on within the university setting and bringing that back to the classroom. The students then bring it back to their homes, so we see the impact of science on daily living as well as on career choices.

Dr. VARMUS. I will emphasize that every Institute has programs not always of the magnitude of NCRR's programs, but many are similar in nature. In addition the Office of the Director, through the Office of Intramural Research, coordinates programs throughout the Institutes to provide intramural training opportunities at NIH. These programs are designed primarily to instruct high school students, college students, and post graduate students in medical science.

NIH is committed to a very large mission that addresses both the recruitment of people into the medical profession and the development of education programs to acquaint the general public with the fruits of biomedical research.

Mr. SMITH. Did you say you made a grant to a public television station?

Dr. VAITUKAITIS. Yes.

Mr. SMITH. They developed this?

Dr. VAITUKAITIS. They developed the modules. I have watched all the modules that they prepared and the series is geared toward kids. It is very distracting to me, but it fits them, since it is made to rap music and it explains basic things well.

DISSEMINATING INFORMATION

Mr. SMITH. That is what I mean by packaging, how you would have to have a different package for them than for the adults.

I just think that TV could be such a wonderful medium and I don't think we package the sound bites that disseminate the information that we are spending billions to acquire in a way that will change people and their life-style.

Dr. LINDBERG. I would like to tell you about at least two other efforts in that direction. Historically one of the early good ones was the National Cancer Institute creation of a PDQ, which is an information service with cancer protocols. Right from the outset the NCI determined to keep the information up to date.

There is a huge editorial board that meets quarterly. One-half of the membership consists of professionals, primarily oncologists, and one-half patients.

This system was put up in partnership with National Library of Medicine as a matter of fact and 98 percent of its use is still through the NLM computer and CD–ROMs.

Now the new program for the Agency for Health Care Policy and Research, where they develop clinical practice guidelines, has been deliberately modeled on the NCI–NLM model. Thus there is a formal section for the practitioner and a formal section for the patient. One, of course, can read either one but it is at least written by professional writers with the hopes that it is expressed properly and patients can understand it.

I only say those two things because a bad job of presenting it to the public can do a lot of harm. I would rather see us do it gradually and use professionals and do it right.

Mr. SMITH. I am afraid that there is a natural tendency for network television stations and radio stations to perhaps exaggerate a little bit, to mislead a little bit to make it a little more interesting that way. And so the public not only may not be getting as much information as we are paying for through research, but not disseminating, but they may also be getting some information they would be better off without and without an offset of good information.

Dr. LINDBERG. There is another factor, too, Mr. Smith. My colleague, Dr. Masys, reminds me there is the 1–800–4–CANCER telephone line at NCI and the hundreds of pamphlets on specific cancers that are aimed at patients.

But I must note some of the dangers of the earnestness with which the volunteer groups and the local associations will just undertake to get the information out.

We object to the fact that there is no bibliographical control. This sounds a little stuffy from a national librarian point of view, but what it amounts to is you encounter a pamphlet that has no date. It has no city where it is published. You are not certain who is responsible for it. You don't know if it is out of date. There is no way to withdraw the information once it is put out there.

I think that what you are urging is exactly right, and I do want you to see that at least some of the parts of NIH have had a long history in disseminating information.

Mr. SMITH. Could you estimate what percent of your $11.5 billion goes for disseminating information?

Dr. VARMUS. I was informed we don't have the precise number; we can provide that information to the Committee at a later time.

Mr. SMITH. Would your efforts be targeted for dissemination to doctors and professionals?

Dr. VARMUS. A large part of it, yes, but that is a very important component.

Mr. SMITH. Well, it is important, but we need to get some information to people other than professionals, too.

Dr. VARMUS. We agree with that.

Mr. SMITH. Staff just points out that last year in the Committee report there was a request that you submit prior to 1995 hearings an identification of the total spending on education activities, clearinghouses, prevention campaigns, outreach efforts, and publications, and they tell me we have not received that yet.

Dr. VARMUS. I am told the report is on its way.

Mr. SMITH. Well, I think that is an important thing and we shouldn't—you know we can get so tied up in our scientific approach to everything.

You said that you gave a grant to a public television station concentrating on children. That is good, to the extent you do it. But should each Institute be doing that or should you have a center that is responsible for looking for information across the whole spectrum and getting it packaged and having in mind the objective of changing life-styles of people who only get sound bites? I mean, is there a better way to do this than what we are doing or have you really thought it through?

Dr. VARMUS. We are doing a couple of things that I think will help here. NIH is in the process of restructuring our Office of Education. The office will have several components including education in the sciences and education to the public. We hope such programs will provide a number of advances along the lines you are suggesting.

We also approach the question through a few other offices that are centrally located in the Office of the Director, NIH. The Office for Prevention Research and Preventive Medicine, under the direction of Dr. William Harlan, provides active coordinated efforts in outreach. Further, the Office of Minority Health Research under the direction of Dr. John Ruffin coordinates programs where there are special needs for addressing the health education of minority communities.

Mr. SMITH. Well, I think these are questions that we need to do some thinking about.

The greatest risk possible for different kinds of diseases that we have in our society are illnesses. I just think we need to spend some time really thinking through this packaging thing, and I emphasize packaging again because it is the way it is packaged that is so important in this society where people don't sit down and read.

A lot of people can't read, as a matter of fact, but they will watch TV if it its attractive enough. Some people only watch the spot announcements. You know they will sit there, and as soon as the spot announcement comes on, they will look at it. They like it. It is packaged in a way that is attractive.

That is when I turn my head the other way, but for a lot of people, that is what they look at, including children, you know. Nice tunes, all that.

Well, I think that is one thing and I would like—I wish you would get that report in and do some thinking about this, of what we can do out there to do a lot better job than we are doing.

Dr. VARMUS. This is a responsibility we share with other agencies including the FDA, and CDC, and the Public Health Service. These are very active concerns. You may want to discuss these concerns with Dr. Lee when you see him later next week.

Mr. SMITH. Do some thinking about how we can do a better job of changing people's life-styles just through information.

I guess that concludes the National Institutes of Health. Thank you.

Dr. VARMUS. Thank you. We appreciate your listening to us.

Mr. SMITH. The Committee will stand adjourned until Thursday morning.

[The following questions were submitted to be answered for the record:]

NATIONAL LIBRARY OF MEDICINE

BASIC LIBRARY SERVICES

Mr. Smith: Have you been able to achieve a balance between investment funding for high performance computing and your ongoing Library services or are your basic operations suffering at the expense of the new initiative?

Dr. Lindberg: Essentially all investment funding received by the National Library of Medicine has been designated by Congress for welcome and important new initiatives, including high performance computing and communications (HPCC), outreach, health services research information, and AIDS information services. During this period, the budget for basic library services has remained flat although demand for these services has increased as have costs. Many of the new investment programs depend on the ongoing services and increase the demand for them. Thus far the Library has been able to respond to the increased demands.

INTERNET

Mr. Smith: Part of the high performance computing initiative is to link medical institutions to Internet. Why is Federal assistance required in this effort--aren't many institutions already on Internet or have sufficient incentive to join without Federal inducements?

Dr. Lindberg: Federal assistance is required to link institutions to the Internet in order to support the initial high costs of acquiring a connection and to demonstrate the various benefits of an Internet connection. It is true that many health institutions are already connected to the Internet, but these are primarily the academic institutions. The great "untapped" clientele are those in hospitals where the majority of health personnel reside. Medical students upon graduation are demanding hospital Internet use because they become dependent upon it in medical school and feel isolated without it. Transferring images via Internet is in its infancy, but when the techniques are perfected it will become universal.

NATIONAL INFORMATION CENTER ON HEALTH SERVICES RESEARCH

Mr. Smith: How much funding will you allocate to the National Information Center on Health Services Research in 1995?

Dr. Lindberg: In FY 1995, the National Library of Medicine plans to allocate $8,188,000 to programs coordinated by the National Information Center on Health Services Research. This represents a 2.4% increase above the $8 million added to NLM's budget in FY 1994 to support the new Information Center.

Mr. Smith: Are all your health services research holdings now available through the center's online database?

Dr. Lindberg: The National Information Center is coordinating the development of a number of new NLM databases designed to serve health services researchers and the many other groups who need better access to the results of health services research. HSTAR (Health Services and Technology Assessment Research), a new bibliographic database which became publicly available in February 1994, is a "one-stop shop" for locating health services research publications, including guidelines and technology assessments, held in the NLM collection. HSTAT (Health Services and Technology Assessment Text), an even newer full-text online service, allows users to search the full-text of practice guidelines and technology assessments produced by AHCPR, NIH, and other PHS agencies. Other databases, including a directory of health services research-in-progress, are under development.

IAIMS PROGRAM

Mr. Smith: Has the nature of the IAIMS Program changed from linking offices within a single medical center to establishing linkages with external databases?

Dr. Lindberg: NLM's Integrated Advanced Information Management Systems (IAIMS) Program continues to provide assistance for information networking within institutions and for connecting externally to other databases and information resources. Internal network capability is required for optimal information access to institutional resources and for widespread access to external resources. As the national information networking capability improves, more and more use of external databases is taking place by institutional users. The IAIMS Program now requires all grantees to include substantial incorporation of one or more elements of High performance Computing and Communications (HPCC) and the National Research and Education Network (NREN) into its information systems.

Mr. Smith: How many medical institutions are interested in an IAIMS grant? How many more years do you envision awarding IAIMS grants?

Dr. Lindberg: Hundreds of academic medical centers, hospitals, and other health science facilities have expressed interest in the IAIMS Program, and are at some stage in planning for a grant application. Inasmuch as the information revolution is just beginning on a large scale in the health sciences, the need for the guidance, encouragement and assistance provided by the IAIMS Program will continue for many years to come in order to meet the national priorities for advanced computing and communication in medicine. The IAIMS Program was significantly revised in 1992 to reflect the great changes taking place in computing and information networking, and to support national initiatives in HPCC and NREN.

OUTREACH PLANNING PANEL

Mr. Smith: You have established a planning panel for a program to train health science librarians. Would this be a new venture for NLM?

Dr. Lindberg: The 1986 NLM Long Range Plan, along with its updates on Outreach (1989), Electronic Imaging (1990), and Toxicology and Environmental Health (1992), recognized the importance of developing a cadre of highly trained health sciences librarians, and other information professionals, to adapt modern information technologies to the needs of the biomedical community. This requirement is also a major underpinning of a key component of the Presidential initiative in High Performance Computing and Communications, which is concerned with the training needs of individuals capable of creating and utilizing emerging computing and networking technologies in the national interest. Platform for Change, a recent planning document prepared by the Medical Library Association, lists areas in which health science librarians believe they will need proficiency in the future.

In the era of health care reform, the role of librarians will change dramatically as the institutions in which they work also undergo dramatic change. New health care networks will require a vast array of information, including clinical and epidemiological data, medical literature and other "knowledge-based information," as well as financial and administrative data. The manager of this information must be able to integrate various sources of information from local and distant sites (often via advanced communications and networking technologies), evaluate its usefulness, and provide it to the user in a timely fashion.

This panel is analyzing the possible programs and activities of the NLM, of individuals, of professional associations, and of other institutions that might be undertaken over the next ten years in order to assure that our society benefits from the skills of health science librarians. NLM also wishes to assure that persons who choose health science librarianship will be properly educated and trained, and that they have an opportunity to engage in the most important work concerning information and health care.

To this end, NLM could act as a catalyst to identify and bring together specific groups that are prepared to take responsibility for a portion of the problem, and to work toward achievement of common goals. The focus would be on innovative planning for the implementation of specific report recommendations deemed to be of exceptionally high priority and that require further study. High priority areas include the role of the librarian in an era of health care reform, library school curricula, lifelong learning, and broadening recruitment into the profession.

MEDLARS ACCESS

Mr. Smith: How are you handling the loss of revenue from your reduced user fees for MEDLINE? Has your appropriation request been increased accordingly?

Dr. Lindberg: MEDLINE user fees were reduced in response to a welcome request from Congress that NLM narrow the definition of the access costs to be recovered from users of MEDLARS data. Some of the categories of costs the Library eliminated involved staff time and computer costs already covered by NLM's appropriation. The decision not to recover these costs has led to a decrease in funds returned to the U.S. Treasury. Other costs no longer recovered, such as contract costs associated with providing online training to health sciences librarians, were paid directly by NTIS from the user fees collected. NLM's appropriation request has not been increased to offset these expenses. The training program has been cut back and some of its costs have been paid by the Library's existing budget. NLM is currently working on a complete redesign of its online training program to see if a less costly program can be implemented using new technologies.

BASIC LIBRARY SERVICES

Mr. Smith: Your budget proposes to reduce Library personnel by 9 staff in 1995. Will this be a problem as your document requests increase, or do you plan to contract out this work?

Dr. Lindberg: Following an A76 study of the document delivery function in 1986, NLM contracted out several document delivery tasks, began a series of planned improvements to the automated systems used for document delivery transactions, and gradually reallocated some inhouse FTE from document delivery to other basic library services. For several years, the combination of contract support and better automated systems has enabled the Library to keep pace with increased document delivery demand while decreasing the number of NLM FTE devoted to this activity. We are now approaching the minimum number of NLM FTE necessary to maintain a high quality document delivery service. There is relatively little document delivery work still handled by NLM staff members that is amenable to contracting out. The Library continues to investigate new ways of providing copies of documents to health professionals quickly and inexpensively. Resolving issues related to the balance between intellectual property rights and user access is as important for the future as staffing considerations. However, the reduction of 9 FTE is difficult to absorb at a time when the demand for basic services increases--be it acquisition, indexing, cataloging, interlibrary lending, or managing automated retrieval systems.

Mr. Smith: Are you having any problems with either your mainframe computer capacity or Library storage capacity?

Dr. Lindberg: NLM had a major upgrade in its computer capacity in 1992. At the present rate of growth, there is adequate mainframe capacity to meet NLM's needs through 1996. We are not now planning any future mainframe upgrades. Future capacity requirements hopefully will be met through smaller systems which can be upgraded in an incremental manner.

The Library estimates that it has sufficient space to accommodate the growth of its collection through the year 2004. This projection assumes that NLM will increase the amount of compact shelving used to house older materials. NLM is currently exploring options, such as offsite storage, to handle growth of the collection beyond the next 10 years.

PRESERVATION

Mr. Smith: How is your collection preservation effort progressing? What share of your valuable collection is currently protected?

Dr. Lindberg: From the preservation perspective, NLM has three types of volumes in its collection: 1) brittle volumes that must be copied to be preserved; 2) acidic volumes that will become brittle unless some corrective action is taken; and 3) volumes made of permanent paper that will not require extraordinary preservation measures. When NLM developed a major preservation plan for its collection in 1985, its first priorities were to increase the pace of microfilming its brittle volumes and to mount a campaign to increase the number of new biomedical publications printed on permanent paper. Since that time, NLM has made slow, but steady progress on microfilming its brittle materials. At the end of FY 1993, 27.4 million brittle pages had been microfilmed or 46% of the estimated 60 million brittle pages found in the NLM collection in the mid-1980s. NLM is now microfilming at the rate of about 7,000 volumes per year. The Library's efforts to increase the use of permanent paper in biomedical journals have been extremely successful. We now estimate that essentially all new substantive U.S. biomedical publications will be printed on alkaline paper by the year 2000.

While progress has been good on the brittle materials and excellent on newly published literature, NLM's mid-80s expectations about the emergence of cost-effective methods for preserving acidic, but not yet brittle volumes have proven to be overly optimistic. The mass deacidification procedures that the Library planned to use for this category of material (which is the bulk of the existing NLM collection) have not progressed as rapidly as estimated and are not suitable for the coated paper that is present in the majority of NLM's volumes. NLM is currently reviewing options and developing cost estimates for handling its acidic, but not yet brittle volumes.

DOCVIEW SYSTEM

Mr. Smith: You are working on a DocView system that would allow the delivery of actual Library documents over Internet rather than abstracts. How many years away is such a system?

Dr. Lindberg: The ability to transmit actual Library documents over the Internet is here today. Using current system software, such as Ariel, libraries are scanning individual documents and transmitting them via the Internet. DocView is a very flexible system for reading, manipulating, and managing machine-readable documents which have been transmitted via Internet using Ariel or another similar software.

What is NOT available today is a large resource of biomedical documents that are already in machine-readable form and can be sent via the Internet without the initial resource-intensive steps of retrieving the requested document from a library shelf and scanning it so it can be transmitted. The major barriers to assembling a large corpus of machine-readable documents for this purpose are the complex intellectual property rights issues involved, the expense of scanning large numbers of documents for which there may be little or no subsequent demand, and, in the case of documents supplied by publishers in machine-readable form, the need to deal with a variety of non-standard document formats. Even if a large resource of machine-readable documents existed today, the majority of health professionals do not yet have the powerful personal computers and the Internet connections necessary to take advantage of it. As many as 75% of the nation's hospitals do not yet have access to the Internet.

Mr. Smith: Must your entire collection be scanned in order for the DocView system to be functional?

Dr. Lindberg: Since documents can be scanned individually for transmission via the Internet to workstations that have DocView or a similar system, NLM's entire collection need not be scanned before such a system becomes functional. To decrease the cost of access to documents over the Internet, however, will require a large resource of documents that are already in machine-readable form. To provide Internet delivery to the majority of U.S. health professionals will require many more sophisticated workstations and Internet connections than currently exist in hospitals and individual offices. In the interim, NLM will continue to experiment with the use of DocView and related technology to deliver the full text of government publications and other documents.

GENBANK

Mr. Smith: What is the budget for the GenBank DNA Sequence Database you operate?

Dr. Lindberg: The annual cost of producing, maintaining, and distributing the GenBank database is approximately $2.9 million. The database is growing at nearly twice the rate it was in 1992, access of online services has risen by a factor of 10, and the database has been enhanced by the addition of protein sequences and Medline citations.

Mr. Smith: Do you charge an access fee?

Dr. Lindberg: No. There are no charges for accessing the GenBank database on the NCBI computers. Users have the choice of downloading the entire database as a series of files by means of the network file transfer program, FTP. Alternatively, they can search for particular GenBank records by sequence comparison searching or by keyword searching through e-mail servers. For users directly connected to the Internet, special client programs are available free from the NCBI which allows users to directly connect to NCBI computers and perform searches interactively over the network.

The only costs associated with GenBank data are for copies of the database on CD-ROM which are released every two months. Subscriptions for the CD-ROM versions of the database are handled through the Government Printing Office. The annual subscription rate is $76 dollars for a version with text retrieval software and linked bibliographic citations from Medline. A single-disk, database-only version is available for $47.

Mr. Smith: Are there any private sector competitors with comparable databases?

Dr. Lindberg: GenBank is part of an international collaboration which consists of partner databases in Europe and Japan, both of which, like GenBank, receive their support from public funds. Through this collaboration, each of the databases collects data from researchers in its own geographical area and, by exchanging data with the collaborators daily, ensures that each database can be a comprehensive source of DNA sequence information. Each of the collaborators provides versions of the database at no cost via network access. Companies in the private sector can and do acquire the sequence data from the public databases and add value in the form of annotation or software and thereby offer a marketable product. There are, however, no known private sector databases which collect or produce the original data which goes into GenBank; instead, private sector sequence databases are derivative of GenBank.

HIGH PERFORMANCE COMPUTING AND COMMUNICATIONS

Mr. Smith: Break out 1994-1995 funding for the high performance computing initiative by component.

Dr. Lindberg: The FY 1994-1995 funding for high performance computing (NLM only) is as follows:

	FY 1994	FY 1995
Extramural	$ 800,000	$ 5,300,000
Intramural	11,585,000	21,685,000

MEDICAL LIBRARY ASSISTANCE PROGRAM

Mr. Smith: Break out 1993-1995 funding for the various components of the Medical Library Assistance Program.

Dr. Lindberg: The FY 1993-1995 funding for the Medical Library Assistance Program is as follows:

	FY 1993	FY 1994	FY 1995
Resources	$1,137,000	$1,114,000	$1,145,000
Connections Program	0	400,000	411,000
RMLs	5,500,000	6,000,000	6,168,000
Training	3,828,000	4,375,000	4,997,000
IAIMS	3,995,000	3,300,000	3,393,000
Other	631,000	494,000	508,000

LITERATURE ACQUISITION

Mr. Smith: What is the 1993-1995 Library acquisition budget?

Dr. Lindberg: The FY 1993-1995 Library acquisition budget is as follows:

FY 1993	FY 1994	FY 1995
$4,089,000	$4,383,000	$4,821,000

NLM REIMBURSEMENTS

Mr. Smith: What are your total 1993-1995 reimbursements from all sources?

Dr. Lindberg: The primary organizations providing funds to the NLM are the Health Care Financing Administration, Department of Commerce, Agency for Toxic Substances and Disease Registry, and Environmental Protection Agency. The expected amounts of reimbursements for FY 1993-1995 are as follows: FY 1993: $11,893,000; FY 1994: $11,814,000; FY 1995: $11,814,000.

HIGH PERFORMANCE COMPUTING AND COMMUNICATIONS

Mr. Smith: Identify government-wide 1993-1995 spending on high performance computing and communications by Federal agency.

Dr. Lindberg: The following is a list of all Federal agencies involved:

Agency	FY 1993	FY 1994	FY 1995
		($ in millions)	
Advanced Research Projects	$254.5	$298.9	$357.4
National Science Foundation	225.2	267.0	328.6
Department of Energy	99.5	122.2	125.4
National Aeronautics and Space Administration	81.6	113.0	124.9
National Institutes of Health	47.2	57.8	81.8
National Security Agency	0.0	40.2	40.1
National Institute off Standards and Technology	2.1	18.1	56.4
National Oceanic and Atmospheric Administration	9.8	10.8	25.3
Environmental Protection Agency	8.0	7.9	14.7
TOTAL	727.9	935.9	1,154.6

NATIONAL INFORMATION CENTER ON HEALTH SERVICES RESEARCH

Mr. Porter: In 1993, the NIH reauthorization legislation created the National Information Center for Health Services Research and Health Care Technology. Tell us how this fits in with the Library's services and what accomplishments and future plans you have for this center.

Dr. Lindberg: The new National Information Center on Health Services Research and Health Technology's programs coordinate and supplement related work carried out in other NLM Divisions. It builds upon and expands NLM's existing health information infrastructure. The overall goals of the new Information Center are:

(1) to make the results of health services research, including practice guidelines and technology assessments, readily available to health care practitioners, health care administrators, health policy makers, payers, and the information professionals who serve these groups;

(2) to improve access to information needed by the creators of health services research; and

(3) to contribute to the information infrastructure needed to foster patient record systems that can produce useful health research data as a by-product of current health care.

The Information Center's initial priority is to move to full implementation of the recommendations in the 1991 Institute of Medicine (IOM) study "Improving Information Services for Health Services Researchers: A Report to the National Library of Medicine." Current activities are focused in three general areas:

(1) more rapid development and deployment of new health services research information products and services.

- o in February 1994, HSTAR (Health Services and Technology Assessment Research), a new bibliographic database covering technical reports as well as journal articles and books, became available.

- o in April 1994, the full-text of AHCPR practice guidelines, NIH Consensus Development Statements, the PHS Guide to Clinical Preventive Services, NIH Technology Assessments, and eventually AHCPR technology assessments will become available in a variety of formats designed to ensure that all NLM users have access to them.

- in summer 1994, HSRProj, a database of information on Health Services Research in progress, will become available.

- MEDSTATS, an expert system that helps users to identify sources of answers to statistical questions, is currently in beta-test.

- also under development:

  --special Grateful Med screens to facilitate access to all NLM health services research databases.

  --a database of data-sets useful in the conduct of health services research.

(2) expanded Outreach and training efforts to promote effective use of new services and to reach new user groups.

- formal user testing of new products and services, such as HSTAR and full- text access to clinical practice guidelines.

- a baseline study of current use of NLM and National Network of Libraries of Medicine services in academic health services research programs.

- an expanded program of exhibits and presentations at relevant professional meetings.

- development of a training plan and materials to help health sciences librarians to respond effectively to health services and health policy inquiries, to search and analyze the literature to support guideline development, and to apply their information analysis skills to hospital continuous quality improvement programs.

- better channels for receiving input and feedback from health services researchers, established with assistance from the Foundation for Health Services Research.

(3) support for research aimed at the development of computer-based patient record systems that can generate useful clinical and health services research data as a by-product of current care.

- new NLM/AHCPR cooperative agreement program for research and testing sites for computer-based patient record systems.

- accelerated expansion of the Unified Medical Language System to increase its utility in computer-based patient record systems.

These activities are expanding the range of materials processed for the NLM collection, are providing additional services useful to all NLM users, and are making NLM services better known and more accessible. The effect on basic library services has been to increase both internal processing workloads and the demand for online, reference, and document delivery services. The increased FY 1994 appropriation for health services research has provided NLM a welcome opportunity to improve access to information that is vital to effective health care delivery.

BASIC LIBRARY SERVICES

Mr. Porter: With increasing emphasis on special initiatives like health services research and High Performance Computing and Communications, what is the relationship between these initiatives and basic library services?

Dr. Lindberg: Most special initiatives in which NLM engages have three main connections to NLM's basic library services. First, these initiatives are dependent on NLM's basic library services. In the case of health services research, the core of the relevant peer-reviewed scientific literature is being collected, preserved, cataloged, indexed, and made available through NLM's basic services. NLM has used its new health services research budget to make improvements in access to technical report literature, to develop non-bibliographical databases and services, and to expand outreach to the producers and some of the users of health services research. In the case of the HPCC project, NLM's existing databases and the National Network of Libraries of Medicine document delivery services are heavily used and critically important services that can be used to demonstrate the value of the new technologies.

Second, the new initiatives increase the number of items that the Library must acquire and process and increases the demand for NLM's existing services. To fulfill its health services research mandate NLM is acquiring, preserving, indexing, and cataloging additional literature, which increases processing workloads, and is making its online and document delivery services known to new groups of users, which increases demand. By providing easier or more cost-effective means for accessing NLM's services, the HPCC initiative is also producing increased service demand.

Third, the new initiatives often lead to improvements in existing services, such as better indexing of special types of publications like clinical trials, guidelines, and metanalyses as a result of the increased focus on health services research, or development of new Internet features that add value to existing services as a result of the HPCC work. While also resource-intensive, these improvements are very beneficial to NLM's users.

INTERNET

Mr. Porter: Dr. Lindberg, increasingly institutions, companies and individuals are connecting to the Internet. How is NLM promoting and taking advantage of this development to improve the dissemination and use of research and other health care information?

Dr. Lindberg: NLM and the National Network of Libraries of Medicine have a two-pronged strategy to promote and take advantage of the Internet to deliver useful research-based information at the time and place that health care decisions are made.

First, NLM and network libraries are working together to help medical centers, hospitals, health sciences libraries, and other health-related institutions to connect to the Internet.

- NLM and the National Sciences Foundation co-sponsor a Medical Connections program which has connected about 100 health care institutions in 16 states plus the District of Columbia to the Internet over the past two years.

- With funding from NLM, several regional Medical Libraries in the National Network of Libraries of Medicine are working to connect hospital libraries to the Internet. For example, the University of Washington has assisted eight isolated rural hospitals to the Internet.

- The Regional Medical Libraries also collect and disseminate information about the options for obtaining and funding Internet access that are relevant to health sciences libraries and health care institutions.

A recent survey of members of the National Network of Libraries of Medicine reveal that 75% of the hospitals and 26% of the academic institutions do not yet have access to the Internet. Although progress is being made, there is still considerable work to be done.

Second, NLM and other members of the National Network of Libraries of Medicine are improving the information services available to Internet users. This is done not only by designing new services that take advantage of the special features of the Internet, but also by making existing services, such has MEDLINE, accessible via the Internet and by developing tools that assist users to locate relevant health care information on the Internet.

- Today any NLM online user can use his or her Internet connections to search MEDLINE and other NLM databases and services, usually with a faster response time.

- NLM and other health sciences libraries provide "gopher" servers that help users to find relevant items to transfer via the Internet file transfer protocol and also point to interactive applications such as NLM's online catalog which became available via the Internet in 1993.

- Ftp provides a faster and more cost-effective method for NLM and other network libraries to publish and distribute Clinical Alerts, fact sheets, application forms, sample records, and many publications to users. In January 1994 alone, Internet users made 9,000 document transfers from NLM's ftp server.

- NLM has also used NCSA Mosaic to develop a multi-media Internet-based interface to some information sources including pictorial material.

- In the near future, NLM will expand its Internet services to include several different methods of access to the full text of clinical practice guidelines supported by the Agency for Health Care Policy and Research, as well as NIH consensus development statements and AHCPR and NIH technology assessments.

- As part of its Unified Medical Language System (UMLS) project, NLM is also developing more powerful tools to help users find relevant information among the literally thousands of Internet information resources.

MINORITY PROGRAM

Mr. Stokes: Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Library's programs and activities?

Dr. Lindberg: NLM offers two grants to assist health science institutions in acquiring computer and communications resources towards developing networking infrastructure. The Information Systems Grant can support up to three years at $150,000 per year for some level of networking. The other support is the Internet Connections Grant which can provide up to $30,000 to acquire an Internet connection. For this program NLM mailed announcements to some 1,100 institutional members of the Medical Library Association which includes minority institutions.

Through partnerships with the Historically Black Colleges and Universities (HBCUs), NLM is exploring ways to improve access to its products and services by minority health professionals and by health professionals who serve minority populations and to increase participation in biomedical research by the HBCUs.

Through a collaborative Information Access Project at Meharry Medical College in Nashville, TN over 400 faculty, residents, students and practicing health professionals have been trained to use Grateful Med and MEDLINE. Project funds enabled Meharry to purchase needed computer equipment to connect to NLM's online databases and to provide training on how to search the databases. At the conclusion of the funded project period, participants were eager to remain connected to NLM's information resources. At the request of the Meharry Medical College Library, Meharry and NLM entered into a flat-rate outreach agreement that provides continuing access to the NLM databases.

The Toxicology Information Outreach Initiative is strengthening the capacity of nine HBCUs to train medical and other health professionals in the use of toxicological, environmental, occupational, and hazardous waste databases at NLM. The target audience for the program covers about 90% of medical and other health professional graduates in HBCUs. Pilot strategies are being developed to utilize these HBCUs as vital information channels to reach minority and underserved populations who are disproportionately exposed to hazardous materials at home and in the workplace. In cooperation with the Agency for Toxic Substances and Disease Registry, training and online access have been provided for 27 additional HBCUs with programs and concerns in the environmental and hazardous waste areas. A second phase planned in this outreach initiative is to enhance the existing high-speed Internet connectivity at these collaborating institutions so that biomedical researchers will have full access to the myriad of remote text and image information resources that are available to colleagues at majority institutions. Additionally, as NLM begins to focus outreach efforts in the area of HIV/AIDS information, the methods and approaches used in the Toxicology Information Outreach Initiative will be expanded to include the AIDS-related databases that NLM makes available. A training class, composed primarily of HBCU nursing staff and faculty, scheduled to be held at Howard University on May 17-19, 1994, will provide an overview and hands-on training for all of the toxicology and environmental health databases and will also provide training on the AIDS databases. This class will be used to gather information to assist in the development of specialized AIDS training materials.

Through an Undergraduate Research Study Program begun in 1991, NLM's Lister Hill Center for Biomedical Communications has been training college students majoring in electrical engineering at HBCUs. The students who are chosen through an open competition for sophomore engineering students are awarded two-year academic scholarships that include two summer internships at NLM and continuing R&D assignments during the school year. The first group of three students graduated in the spring of 1993, and a second group of five students had their first summer internship at NLM.

On a continuing basis NLM seeks minority research assistants for research grants, helps program grant directors recruit minority trainees, reaches out to minority institutions through the HBCU initiative, encourages area grant applications from small institutions with high minority student enrollment, and provides supplemental funds for minority students at all levels under the MARC program.

Mr. Stokes: Explain the proposed funding for the programs of the Library that are designed to increase the participation of underrepresented minorities in its research, and research training?

Dr. Lindberg: NLM participates in the trans-NIH Programs of recruiting and training individuals from underrepresented minority groups in its regular Medial Informatics Research Training programs, and in providing supplements to Research Grants to support such individuals. Communications are sent to Training Program Directors encouraging the recruitment of underrepresented minorities. Some Research Grants are awarded to investigators at minority institutions.

In addition to the programs specifically targeted at HBCUs that are described above, and grant activities already described, NLM has an active outreach program directed at increasing participation of underrepresented minorities:

In the spring and summer 1993, NLM staff held a series of outreach discussion meetings in six southern states. The purposes of these meetings were: 1) to establish linkages with key governmental, health, academic and local community organizations that are concerned with the health needs of pregnant women and children in the southern states, and 2) to identify ongoing and planned health programs in which access to NLM's databases could become an integral part of the locally originated programs. A special emphasis was placed on programs that serve minority and rural populations. The Texas Department of Health (TDH) is taking the lead in developing a pilot project to bring NLM's resources to a broad group of health professionals. This effort focuses on making access to biomedical information easier and more readily available to a diverse group of health professionals engaged in addressing public health concerns in the Texas-Mexico border area of southern Texas, an area that is geographically remote and in which information resources are scarce.

In addition, the University of Texas Health Science Center at San Antonio continues to provide outreach information services to hospitals in the Lower Rio Grande Valley through the Circuit Library Health Information Network. Although she no longer resides in the Valley, Ms. Mary Jo Dwyer continues to serve as the circuit librarian providing information services through use of an 800-number phone line and monthly visits to the circuit institutions.

Through the National Network of Libraries of Medicine (NN/LM), NLM has provided funds to design and implement a pilot project to improve the status of libraries and the information services they provide to health professionals in the Lower Mississippi Delta. Libraries without onsite access to NLM's databases in any form and that were not participating in DOCLINE (an electronic means for interlibrary loan of documents) were identified as candidate institutions to receive computer hardware and software, a fax machine, possible subsidization of access costs, and training and other support. Thus far, support has been provided to 9 libraries in Arkansas, 9 libraries in Louisiana, 2 libraries in Mississippi and 3 libraries in Missouri.

Other new outreach efforts include several intended to reach health professionals who serve Native American populations:

- University of South Dakota. Thirty-one rural community centers and rural clinics in South Dakota that serve Native American populations on or near reservations are the focus of this Grateful Med project.

- Marshfield Medical Research Foundation, Marshfield, WI. This Grateful MED project targets primary health care providers serving native Americans in rural Northern and Central Wisconsin.

- Salish Kootenai (Tribal) College, Pablo, MT. An Information Access Grant was awarded to this college on the Flathead Indian Reservation to enable the library to become a member of the Western Montana Medical Libraries Access network which is implementing a Grateful Med project.

Mr. Stokes: How does your institute identify its priorities for investments in minority research and research training, and outreach?

Dr. Lindberg: Grant support of projects at minority institutions or by minority investigators has been, and continues to be, a priority of the NLM. Many grants for information networking and outreach have involved minority institutions and members; information access by underserved populations is an ongoing priority.

HIGH PERFORMANCE COMPUTING AND COMMUNICATIONS

Mr. Stokes: The NIH FY 1995 budget request includes $81.8 million, or a $24 million increase, for high performance computing. How will the major initiatives under the purview of your institute benefit from this investment?

Dr. Lindberg: The application of information technologies derived from the HPCC program has the potential to significantly improve health care delivery. Every health care professional needs knowledge of the scientific basis of health and disease, as represented in the published medical literature and in scientific databanks and patient-specific information, such as laboratory test results, x-rays, and the record of previous findings and prior medical care. Although systems such as MEDLINE which permit rapid searching of the medical literature nationwide, most of the information sources for healthcare are inadequate. Medical records are primarily hand written paper records; subject to being lost or misplaced. Patients consulting several physicians usually have several fragmentary records in the offices of each of those providers. Existing laboratory computer systems and radiology computer systems and administrative computer systems in hospitals and clinics, are usually connected only by paper printouts. With the availability of advanced information technologies, the lack of coordinated and connected information systems is inexcusable.

The HPCC program will focus on research and development of solutions to these problems: integrated information systems which incorporate both scientific and patient-specific clinical information, and make it available to health professionals in a distance-independent electronic form over high speed networks, while protecting security and privacy. In FY 1993 and FY 1994, NLM made competitive research contract awards for testbed networks for linking hospitals, clinics, doctor's offices, medical schools, medical libraries, and universities to enable health care providers and researchers to share medical data and imagery. A variety of rural and urban projects were funded in West Virginia, Pennsylvania, Indiana, Illinois, Iowa, Kansas, Oregon, and California. These projects will create and evaluate advanced methods for managing healthcare information, and provide models and standards for deployment of such systems nationwide.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES

Mr. Stokes: What are some of the major initiatives underway at your Institute to increase the participation of Historically Black Colleges and Universities in Biomedical Research?

Dr. Lindberg: Through partnerships with the Historically Black Colleges and Universities (HBCUs), NLM is exploring ways to improve access to its products and services by minority health professionals and by health professionals who serve minority populations and to increase participation in biomedical research by the HBCUs.

Through a collaborative Information Access Project at Meharry Medical College in Nashville, TN over 400 faculty, residents, students and practicing health professionals have been trained to use Grateful Med and MEDLINE. Project funds enabled Meharry to purchase needed computer equipment to connect to NLM's online databases and to provide training on how to search the databases. At the conclusion of the funded project period, participants were eager to remain connected to NLM's information resources. At the request of the Meharry Medical College Library, Meharry and NLM entered into a flat-rate outreach agreement that provides continuing access to the NLM databases.

The Toxicology Information Outreach Initiative is strengthening the capacity of nine HBCUs to train medical and other health professionals in the use of toxicological, environmental, occupational, and hazardous waste databases at NLM. The target audience for the program covers about 90% of medical and other health professional graduates in HBCUs. Pilot strategies are being developed to utilize these HBCUs as vital information channels to reach minority and underserved populations who are disproportionately exposed to hazardous materials at home and in the workplace. In cooperation with the Agency for Toxic Substances and Disease Registry, training and online access have been provided for 27 additional HBCUs with programs and concerns in the environmental and hazardous waste areas. A second phase planned in this outreach initiative is to enhance the existing high-speed Internet connectivity at these collaborating institutions so that biomedical researchers will have full access to the myriad of remote text and image information resources that are available to colleagues at majority institutions. Additionally, as NLM begins to focus outreach efforts in the area of HIV/AIDS information, the methods and approaches used in the Toxicology Information Outreach Initiative will be expanded to include the AIDS-related databases that NLM makes available. A training class, composed primarily of HBCU nursing staff and faculty, scheduled to be held at Howard University on May 17-19, 1994, will provide an overview and hands-on training for all of the toxicology and environmental health databases and will also provide training on the AIDS databases. This class will be used to gather information to assist in the development of specialized AIDS training materials.

Through an Undergraduate Research Study Program begun in 1991, NLM's Lister Hill Center for Biomedical Communications has been training college students majoring in electrical engineering at HBCUs. The students who are chosen through an open competition for sophomore engineering students are awarded two-year academic scholarships that include two summer internships at NLM and continuing R&D assignments during the school year. The first group of three students graduated in the spring of 1993, and a second group of five students had their first summer internship at NLM.

On a continuing basis NLM seeks minority research assistants for research grants, helps program grant directors recruit minority trainees, reaches out to minority institutions through the HBCU initiative, encourages area grant applications from small institutions with high minority student enrollment, and provides supplemental funds for minority students at all levels under the MARC program.

GS-15 AND ABOVE POSITIONS

Mr. Stokes: How many GS-15 and above positions are there in your institute?

Dr. Lindberg: There are 46 GS-15 and above positions at NLM.

Mr. Stokes: How many employees at the library are in GS-15 and above positions?

Dr. Lindberg: There are currently 38 employees in GS-15 and above positions.

Mr. Stokes: At the library, currently, how man African Americans are at the GS-15 and above level?

Dr. Lindberg: There are currently 3 African Americans at the GS-15 and above level.

Mr. Stokes: In what positions are they?

Dr. Lindberg: The 3 positions are as follows: Deputy Director for the Lister Hill National Center for Biomedical Communications, Chief, Biomedical Information Services Branch for the Division of Specialized Information Services, and Materials Development Officer.

Mr. Stokes: For the library, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level?

Dr. Lindberg: Currently, the NLM has no requests for exceptions to the freeze.

Mr. Stokes: Has the NIH requested relief from the freeze, if so, what was the response?

Dr. Lindberg: The NIH requested relief from the Public Health Service hiring freeze imposed in December 1993 because NIH had successfully managed its FTE ceiling. The request is under consideration by the PHS.

Mr. Stokes: If the freeze were lifted, how would it help the EEO problem in your institute?

Dr. Lindberg: The library's efforts to recruit and its ability to hire minority individuals would be enhanced if the freeze were lifted. An immediate benefit would be NLM's intramural Associate Program. This program, operating since 1977, offers one year of postgraduate training in medical library/information science to a limited number of medical librarians with a Master's Degree or higher. Each graduate is expected to assume a senior position in a medical library upon completion of the program. NLM is fortunate to have within the current group of associates a number of outstanding minority librarians. The continuing freeze will prevent NLM from hiring any of these individuals before they find permanent employment elsewhere.

The hiring freeze is also affecting NLM's ability to offer the Associate Program to a new group of librarians. NLM is conducting a peer review process for selecting new training associates and preparing to request an exception to the freeze for the anticipated appointments. An additional exception request is being prepared for the hiring of a minority computer support staff.

SUPPORT FOR MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by the Library?

Dr. Lindberg: NLMś level of support for minority institutions for FY 1994 is approximately $1,000,000. This figure includes the Undergraduate Research Study Program, the toxicology outreach initiative, grants to minority institutions and individuals, projects undertaken through the National Network of Libraries of Medicine (NN/LM), and evaluations of outreach intervention strategies.

INTERNET

Mr. Stokes: What is status of initiatives designed to electronically network health care professionals to Internet? What are the projected benefits of this linkage? What is being done to ensure that minority medical institutions are linked to Internet?

Dr. Lindberg: For the third consecutive year NLM is collaborating with the National Science Foundation to offer grants for health science institutions to connect to the Internet. As more and more institutions are linking to the Internet, there is better opportunity to collaborate with colleagues and thus improve communications. The Internet capabilities to transfer files and to access distant resources present a wealth of information to health professionals. Internet offers the ability to conduct distant learning without being required to leave the worksite. Continuing education opportunities will thus be enhanced via Internet. Minority medical institutions were sent program announcements of the Internet Connections Program.

Mr. Stokes: What can you tell us about the objectives and goals of NLM's National Information Center on Health Services Research and Health Care Technology?

Dr. Lindberg: The overall goals of the new National Information Center on Health Services Research and Health Technology are:

(1) to make the results of health services research, including practice guidelines and technology assessments, readily available to health care practitioners, health care administrators, health policy makers, payers, and the information professionals who serve these groups;

(2) to improve access to information needed by the creators of health services research; and

(3) to contribute to the information infrastructure needed to foster patient record systems that can produce useful health research data as a by-product of current health care.

The new Information Center replaces and expands upon the previous NLM Office of Health Services Research Information which was established in 1990 in response to a mandate within the legislation that created the Agency for Health Care Policy and Research. The Center's program will coordinate and supplement, rather than duplicate, related work carried out in other NLM Divisions.

The Information Center's initial priority is to move to full implementation of the recommendations in the 1991 Institute of Medicine (IOM) study "Improving Information Services for Health Services Researchers: A Report to the National Library of Medicine." Current activities are focused in three general areas:

(1) more rapid development and deployment of new health services research information products and services.

- in February 1994, HSTAR (Health Services and Technology Assessment Research), a new bibliographic database covering technical reports as well as journal articles and books, became available.

- in April 1994, the full-text of AHCPR practice guidelines, NIH Consensus Development Statements, the PHS Guide to Clinical Preventive Services, NIH Technology Assessments, and eventually AHCPR technology assessments will become available in a variety of formats designed to ensure that all NLM users have access to them.

- o in summer 1994, HSRProj, a database of information on Health Services Research in progress, will become available.

- o MEDSTATS, an expert system that helps users to identify sources of answers to statistical questions, is currently in beta-test.

- o also under development:

  --special Grateful Med screens to facilitate access to all NLM health services research databases.

  --a database of data-sets useful in the conduct of health services research.

(2) expanded Outreach and training efforts to promote effective use of new services and to reach new user groups.

- o formal user testing of new products and services, such as HSTAR and full-text access to clinical practice guidelines.

- o a baseline study of current use of NLM and National Network of Libraries of Medicine services in academic health services research programs.

- o an expanded program of exhibits and presentations at relevant professional meetings.

- o development of a training plan and materials to help health sciences librarians to respond effectively to health services and health policy inquiries, to search and analyze the literature to support guideline development, and to apply their information analysis skills to hospital continuous quality improvement programs.

- o better channels for receiving input and feedback from health services researchers, established with assistance from the Foundation for Health Services Research.

(3) support for research aimed at the development of computer-based patient record systems that can generate useful clinical and health services research data as a by-product of current care.

- o new NLM/AHCPR cooperative agreement program for research and testing sites for computer-based patient record systems.

- accelerated expansion of the Unified Medical Language System to increase its utility in computer-based patient record systems.

These activities are expanding the range of materials processed for the NLM collection, are providing additional services useful to all NLM users, and are making NLM services better known and more accessible. The effect on basic library services has been to increase both internal processing workloads and the demand for online, reference, and document delivery services. The increased FY 1994 appropriation for health services research has provided NLM a welcome opportunity to improve access to information that is vital to effective health care delivery.

Mr. Stokes: The human genome mapping and sequencing initiative offers tremendous hope for information highways to understanding diseases and disorders. What is NLM's role in this NIH effort?

Dr. Lindberg: By producing GenBank, NCBI provides fast and comprehensive access to some 50,000 human sequences and related biological annotation. NCBI has engineered new network retrieval tools to permit genome researchers to conduct rapid and accurate searches of new sequences against the complete database in under 15 seconds. The database searching facility at NCBI has enabled laboratories to rapidly interpret the vast quantities of data that are produced as part of the human genome initiative. Genome research centers in Boston, Rockville, St. Louis, Houston, Utah, Oklahoma, San Diego and other locations use NCBI's BLAST search service to identify coding regions of genes and assign probable biological functions.

Staff scientists at NCBI who are skilled in sequence analysis have been key collaborators in experimental work on the hereditary colon cancer gene and genes responsible for neurofibromatosis and Kallmann syndrome. NCBI's database of "Expressed Sequence Tags" (dbEST) is now the recognized depository for the information resulting from the rapidly growing area of research on expressed gene sequences (cDNAs), a rapid method for identifying partial gene sequences. Over 30,000 sequences have been deposited in its first year of operation.

Other network tools have been designed to allow keyword searches of GenBank data and automated retrieval of literature references that are topically related. These search tools have been used by over 20,000 different researchers in the past year who have conducted nearly 2 million searches of the database. Although individual human genome centers have their own informatics staff, their work focuses on organizing and analyzing the centers' local data. NLM's role is in ensuring that the public data from these centers and from hundreds of smaller research groups is made available to all biologists in a form that is readily accessible and biologically accurate.

Mr. Stokes: What are some of the most exciting and most promising research opportunities at the Library? Elaborate on the benefits to be received from further investments in this research.

Dr. Lindberg: As biomedical researchers are increasingly finding computers to be an essential part of their work, practitioners of medicine are also beginning to realize the value of these important tools. The clinically significant genetic tests they must deal with, the need to educate their patients about genetic and metabolic family afflictions, these and many other examples demand better systems for continuing medical education, for personal proficiency in information search and retrieval, and for improved systems to structure medical knowledge. Fortunately, these needs are corresponding with increasing capability on the computer side. New computer and communications technologies will have a wide ranging and beneficial impact on biomedical research and healthcare. Technology has made possible our present medical information databases consisting of references and abstracts. However, much of the understanding of complicated processes of health and disease lies in images--pictures of body systems, organs, and molecules--that cannot effectively be described in words. References can be sent from the National Library of Medicine to a health professional anywhere in the United States in seconds. It would require several hours to send just one black and white x-ray picture at high resolution if we were limited to present-day ordinary telephone lines. We need an advanced national information infrastructure capable of quickly transmitting these and other forms of computer-based medical information. High Performance Computing and Communications (HPCC) technologies are building powerful computers to store and analyze biomedical scientific data and are extending high speed computer networks to create an national electronic community of health professionals. Over these high speed digital highways, scientists can quickly collaborate and share new findings, and practicing health professionals can instantly access medical databanks and exchange clinical data for the efficient care of patients. Major ventures are underway to improve access to information which can prevent disease and alleviate suffering in minorities, women, and children, to discover the genetic basis of disease, and to ensure that the findings of health services research can be translated into better, more affordable health care.

Recent HPCC accomplishments include the creation and publication on CD-ROM of a prototype Metathesaurus, Semantic Network, and Information Sources Map as part of the Unified Medical Language System (UMLS) research effort to link together computer-based biomedical information resources. Additionally, NLM's "Visible Human" project to acquire the three-dimensional digital representation of a human male and female at millimeter-level resolution, derived from computed tomography, magnetic resonance imaging, and digitized cryosections, will become available nationally via the Internet in 1994.

NLM recently awarded grants for 10 Medical Informatics Training Grant programs at academic medical centers. The program supports cross-disciplinary training of health professionals in the use of advanced computing technologies. A Medical Connections program in collaboration with the National Science Foundation is providing support for medical centers to connect to the Internet. An important new program will be launched in FY 1994 through a Cooperative Agreement in the general area of the Electronic Medical Record System. NLM will be joined by the Agency for Health Care Policy and Research (AHCPR) in sponsoring the Cooperative Agreement.

Under the NLM HPCC Broad Agency Announcement (BAA), awards are being made in FY94 in the areas of virtual reality for medicine and collaborative technology for real time treatment of patients. These projects will explore areas such as development of organ models for virtual surgery simulation, teleradiology, and teledermatology. Other BAA awards are funding testbed networks for linking hospitals, clinics, doctors' offices, medical schools, medical libraries, and universities to enable health care providers and researchers to share medical data and imagery. One of these is to a consortium of West Virginia institutions to install a system that applies advanced networking technologies to delivering health care in both rural and urban areas of the state.

The successful outcome of these projects will have obvious implications for containing health care costs while raising the quality of patient care.

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of the Library?

Dr. Lindberg: NLM supports ten Research Training Programs in Medical Informatics that are doing much to meet the current need for such researchers, but the demand for trained researchers will continue to grow as advanced technologies are increasingly a part of the health sciences. Of immediate importance, there is a large unmet need for trained individuals to provide leadership in the application and deployment of advanced technologies in health science institutions and facilities. NLM also needs to expand its programs to plan and operate advanced information and communication systems in health science institutions as the availability of such systems will provide daily experience for all researchers and other personnel who use them.

JOURNALS

Ms. DeLauro: What is the process for getting journals on line?

Dr. Lindberg: The Literature Selection Technical Review Committee (LSTRC), an NIH-chartered Committee of experts in biomedical and health-related fields, reviews journals and rates them according to scientific merit and importance to the Index Medicus/MEDLINE audience, based on published selection factors. (A copy of the Journal Selection Fact Sheet is attached.) Journals that are highly rated by this Committee are added to Index Medicus and MEDLINE or other appropriate NLM database. All new journals with indexable articles that are received by NLM are referred to the LSTRC for review after several issues have been published. Individual older journals that were previously reviewed and not rated highly enough to be recommended for indexing will be re-reviewed after two-four years if such a re-review is requested. NLM also enlists the aid of relevant professional societies to review journals in two or three subject areas per year to identify the most substantive and useful journals in an area that should be indexed. In these subject reviews, professional societies are asked to rank all journals published in a subject area, including those already in NLM's online databases as well as newer and older journals in the same subject area that are not currently indexed by the Library. The LSTRC reviews the reports from the professional societies and recommends journals that should be added or removed from the online databases. The LSTRC typically reviews more than 300 individual journals each year, in addition to the results of two to three subject reviews. In FY 1993, LSTRC rated 71 journals highly enough for addition to Index Medicus/MEDLINE.

Ms. DeLauro: I understand that it is difficult to obtain literature on women's health research using classical searches through MEDLINE. Why haven't special efforts been made to include women's health journals?

Dr. Lindberg: All new journals with indexable articles received by NLM, including women's health journals, are referred to the Literature Selection Technical Review Committee, the NIH-chartered Committee of experts in biomedical and health-related fields that advises NLM on the selection of journals for its online databases. NLM adds journals to Index Medicus/MEDLINE and other NLM databases based on the rating assigned by this Committee. Of course, many journals not specifically devoted to women's health issues report the results of research on women's health issues.

In addition to the journal coverage in Index Medicus/MEDLINE, NLM is working to improve other factors that may affect a user's ability to retrieve citations to literature on women's health research. These factors include: the terminology used to index articles; the consistency with which gender-related concepts are identified and indexed; and the extent to which the gender of participants in research studies is identified in the articles publishing results of the studies. As part of its ongoing support to the NIH Office of Research in Women's Health, NLM has reviewed and modified its Medical Subject Headings (MeSH) terminology related to women's health and is examining its indexing practices in this area. The Library is also collecting examples of articles that do not specifically state the gender of study participants for use in discussions of this issue with journal editors.

Ms. DeLauro: Please provide a list of requests made this year by organizations seeking to get their journals on line.

Dr. Lindberg: NLM does not maintain a chronological file of requests from organizations and individuals seeking to have journals indexed in the Library's online databases. Our correspondence is organized by the journal title involved since this arrangement makes it easier to review all requests related to a particular journal. It is not uncommon for the Library to receive several letters from different organizations or individuals related to the same journal. Since the Literature Selection Technical Review Committee (LSTRC) which advises NLM on the selection of journals to be indexed in its online databases typically reviews a journal after several issues have been published, correspondence related to a particular title may be received in more than one year. A number of U.S. and international publishers include requests to NLM that a new journal be indexed as part of their regular marketing plan for every new journal on a biomedical or health-related topic. NLM receives more than 750 requests related to specific journals each year. New indexable journals that are in subject areas covered by NLM's databases are reviewed by the LSTRC irrespective of whether NLM has received correspondence on their behalf, however, and all journals are rated according to scientific merit and importance to the Index Medicus/MEDLINE audience.

HIGH PERFORMANCE COMPUTING AND COMMUNICATIONS

Mr. Bonilla: Could you provide the list of the 11 additional HPCC health related applications that were recently announced?

Dr. Lindberg: The NLM is sponsoring research and development of advanced computing and communications systems for health care as part of its ongoing HPCC program. Ten projects involving twelve research groups will be supported. These projects are divided into the following four research categories:

Research Category 1 - Testbed Networks

Title: Toward a National Collaboratory for Healthcare Informatics

Objective: This project is a collaboration between three medical informatics research groups to build Internet-accessible shared systems which support computerized patient records, clinical research protocols, medical vocabulary servers, teleconferencing, and health professions education.

- Trustees of Columbia University of the City of New York
  New York, NY
- Brigham & Women's Hospital
  Boston, MA
- The Board of Trustees of the Leland Stanford Junior University
  Stanford, CA

Title: A Pilot Indianapolis-Wide 10 Megabit Network for Patient Care and Research

Objective: This project will employ a variety of digital networking technologies to tie together a major teaching hospital with community clinics and pharmacies, providing access to a computerized patient record system, computerized prescriptions, and online medical knowledge sources. The evaluation component of this project will assess the cost and patient outcomes changes which result from the use shared medical information.

- Indiana University
  Indianapolis, IN

Title: A Chicago Metropolitan Medical Network

Objective: This award represents a planning phase which is part of a new facility development plan for Northwestern Memorial Hospital. State of the art internal networks in the new medical center complex will be linked to primary care locations in the metropolitan area. Both scientific and patient-specific clinical information will travel over the network.

- Northwestern Memorial Hospital
  Chicago, IL

Title: A High Performance Testbed Network for Telemanagement of Neuro-Imaging

Objective: A high performance wide area network will be used to transmit neuro-radiology images for consultation, patient monitoring, and shared clinical management. The project will examine the patient outcomes which result from use of digital networks to transmit Computed Tomography and Magnetic Resonance Imaging of the brain and spinal cord.

- The Regents of the University of California
  San Francisco, CA

Title: Iowa Testbed Network

Objective: This project will use the newly developed state-wide digital network in Iowa for creation of a Telecommunications Health Education Resource Center, linking of three hospital sites, improved information services for rural healthcare providers, and several telemedicine prototype systems.

- The University of Iowa
  Iowa City, IA

Research Category 3 - Virtual Reality for Medicine

Title: Organ Modeling in Support of Virtual Surgery Simulation

Objective: This project will create and evaluate advanced computer simulations of human anatomic structure which support surgical planning and health professions education.

- University of Pennsylvania
  Philadelphia, PA

Research Category 4 - Collaborative Technology for Real Time Treatment of Patients

Title: A Comprehensive Teledermatology Program

Objective: Remote diagnosis of skin lesions via teleconsultation to underserved rural ares will be developed and tested in five primary care clinics in Oregon and Kansas.

- Oregon Health Sciences University
  Portland, OR

Title: Implementation of a Teleradiology System to Enhance Consultative Services between Primary and Secondary Care Hospitals and a Tertiary Care Facility

Objective: This project will link six outlying hospitals in western Pennsylvania with the University of Pittsburgh Medical Center for teleradiology to improve neurosurgery, neurology, trauma and critical care. The impact of the system on patient outcomes will be studied.

- University of Pittsburgh
  Pittsburgh, PA

Title: Collaboration Technology for Real-time Treatment of Patient in West Virginia

Objective: A consortium of nine institutions led by the Concurrent Engineering Research Center of the University of West Virginia will build and evaluate a regional telemedicine system for rural areas of the state.

- West Virginia University Research Corp. on Behalf of West
  Virginia University
  Morgantown, WV

Research Category 5 - Information Access

Title: Linking Images to a Clinical Information System

Objective: This project will develop automated text analysis methods to link the textual component of an existing computerized patient record system with a new computerized system for diagnostic images, including pathology, radiology, MRI, and ultrasound.

- University of Pittsburgh
  Pittsburgh, PA

RURAL OUTREACH

Mr. Bonilla: Last year we talked about rural outreach. Because of the geographic nature of my congressional district, it is 58,000 square miles, I am particularly interested in outreach activities conducted by the NLM. What programs are occurring in NLM outreach? Anything new?

Dr. Lindberg: In the spring and summer 1993, NLM staff held a series of outreach discussion meetings in six southern states which included Texas. The purposes of these meetings were: 1) to establish linkages with key governmental, health, academic and local community organizations that are concerned with the health needs of pregnant women and children in the southern states, and 2) to identify ongoing and planned health programs in which access to NLM's databases could become an integral part of the locally originated programs. A special emphasis was placed on programs that serve minority and rural populations. At the meeting held in Austin, Dr. David R. Smith, Texas Commissioner of Health, suggested that the Texas Department of Health (TDH) take the lead in developing a pilot project to bring NLM's resources to a broad group of health professionals. Public Health Regions 8, 9, 10 and 11 comprise the defined target area. This effort focuses on making access to biomedical information easier and more readily available to a diverse group of health professionals engaged in addressing public health concerns in the Texas-Mexico border area of southern Texas. At the present time, the Texas Department of Health is beginning to provide Internet access to its public health regions. The integration of access to NLM's databases and resources dovetails with the installation of the new telecommunications technology to bring medical information to a part of Texas that is geographically remote and in which information resources are scarce. The TDH Library is being aided in its effort by the medical libraries at the University of Texas Health Science Center at San Antonio, the Texas Medical Association, and the Texas Tech University Health Sciences Center.

In addition, the University of Texas Health Science Center at San Antonio continues to provide outreach information services to hospitals in the Lower Rio Grande Valley through the Circuit Library Health Information Network. Although she no longer resides in the Valley, Ms. Mary Jo Dwyer continues to serve as the circuit librarian providing information services through use of an 800-number phone line and monthly visits to the circuit institutions.

Through the National Network of Libraries of Medicine (NN/LM), NLM has provided funds to design and implement a pilot project to improve the status of libraries and the information services they provide to health professionals in the Lower Mississippi Delta. Libraries without onsite access to NLM's databases in any form and that were not participating in DOCLINE (an electronic means for interlibrary loan of documents) were identified as candidate institutions to receive computer hardware and software, a fax machine, possible subsidization of access costs, and training and other support. Thus far, support has been provided to 9 libraries in Arkansas, 9 libraries in Louisiana, 2 libraries in Mississippi and 3 libraries in Missouri.

Other new outreach efforts include several intended to reach health professionals who serve Native American populations:

- University of South Dakota. Thirty-one rural community centers and rural clinics in South Dakota that serve Native American populations on or near reservations are the focus of this project.
- Marshfield Medical Research Foundation, Marshfield, WI. This project targets primary health care providers serving native Americans in rural Northern and Central Wisconsin.
- Salish Kootenai (Tribal) College, Pablo, MT. An Information Access Grant was awarded to this college on the Flathead Indian Reservation to enable the library to become a member of the Western Montana Medical Libraries Access network which is implementing a Grateful Med project.

OUTREACH

Mr. Bonilla: How much will NLM spend in fiscal year 1994 for outreach? Compared with 1993? How much is proposed in the fiscal year 1995 budget?

Dr. Lindberg: The FY 1993-1995 funding for outreach is as follows:

FY 1993	FY 1994	FY 1995
$6,544,000	$6,333,000	$6,500,000

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

UPDATED PLAN FOR THE HUMAN GENOME PROJECT

Mr. Smith: What are the major differences between your original five-year plan and the new plan published last fall? In which areas are you ahead of schedule and where have you fallen behind? Has the $3 billion cost estimate for the project changed?

Dr. Collins: The major differences between the two plans are that the new plan projects three years further into the future and that we now have a much clearer idea of how we will reach our goals and greater confidence that it can be done.

In genetic mapping we have already reached the original five year goal and will now focus on improving the quality of the map. We will also develop improved markers that can be easily used in an automated fashion so that the map will become useful for large scale applications such as mapping risk factors for common diseases.

In physical mapping we are making progress, with respect to the original goal and may surpass it when the five years are up. We will focus on completing the map with markers every 100,000 base pairs on average and on integrating this map with the genetic map and gene maps.

In sequencing we are on target, but it is clear that we must dramatically increase the investment in sequencing technology in the next few years in order to stay on target. Significant improvements in technology and automation over the last three years have given us confidence that the technology needed to sequence the human genome is at hand, but much needs to be done to make it a practical reality. We have also set specific targets for completing the DNA sequence of four of the five model organisms, E. coli, yeast, the fruitfly and the roundworm. These sequences will be essential for deciphering the human DNA. Much has also been learned technologically from the current projects engaged in sequencing model organism DNA and we expect that to continue.

A new goal has been added for gene identification, that is, placing as many of the 100,000 genes on the map as soon as possible. This area was implicitly part of the plan all along, but the technology was not ripe for specific emphasis. Now the time has come to invest in improving this technology and making it robust for genome-wide application.

The cost estimate for the Human Genome Project has not changed with the revised plan. It is still $3 billion over 15 years (in 1991 dollars).

Mr. Smith: Did your original five-year plan call for an intramural program?

Dr. Collins: The intramural program is not considered to be part of the Human Genome Project, per se. Thus it was not included in either the first or the second plan. The intramural program arose out of considerations of the needs of the NIH intramural program and the opportunities it offered for applying the fruits of genome research to medical problems.

COST OF SEQUENCING

Mr. Smith: How far away are you from the goal of bringing sequencing costs down to fifty cents per base pair? Your justification states that "a much larger investment in sequencing technology development is needed." Does your 1995 request meet this need?

Dr. Collins: Since the inception of the Human Genome Project substantial progress has been made toward increasing the throughput and reducing the cost of genomic DNA sequencing. The current cost of genomic sequencing in the most advanced laboratories is approximately one dollar per base pair, and clear paths, based on improvements in automation, molecular biology and informatics, are envisioned that could reduce this cost to the goal of $0.50 per base pair within the next few years. Coupled with new exciting technological opportunities based on systems integration, miniaturization, and increased parallelization, the opportunity exists to advance sequencing technology such that substantially increased throughput and decreased cost can be achieved in the future. The 1995 budget request provides for increased investment in sequencing technology to the extent possible under the overall budget constraints.

NCHGR PRIORITIES

Mr. Smith: How do you respond to the criticism that your first priority should be developing sequencing techniques, not expanding the gene-specific intramural program?

Dr. Collins: This question implies that the intramural program was established at the expense of the extramural program, which is not the case. The allocation of funds for the intramural program was made on a different track from the process for the extramural program and a choice between the two was not part of the process. Within the extramural program we are making every effort to increase the allocation for sequencing technology.

Mr. Smith: How did you decide how much of your funding to allocate to extramural as compared to intramural research?

Dr. Collins: The extramural and intramural budgets were developed entirely separately and with different objectives in mind. The source of the funds was separate as well, so that a question of allocation between the two did not arise. In future years this will no doubt be different, as the two parts of the NCHGR become integrated into the normal NIH process for budget development.

PHYSICAL MAPPING APPROACH

Mr. Smith: French scientists have taken the approach of mapping the entire human genome rather than focusing on particular chromosomes. They now have a rough physical map for the entire genome. Will this change the approach used in the research supported by your Center?

Dr. Collins: The successful French effort is only one example of the way in which technology development under the Human Genome Program has enabled a new, efficient, whole genome mapping strategy. In the U.S., two efforts taking this approach are well under way. The center at the Whitehead Institute in Cambridge, Massachusetts is taking a genome-wide approach to assembling the physical maps of both the human and mouse, while the center at the University of Iowa is constructing a human genetic map using this strategy. The efforts of all these groups have demonstrated the efficiency and cost effectiveness of the genome-wide approach.

It is also important to note that the map that has been published by the French is considerably less detailed than the map called for in the new 5-year plan. The Whitehead center alone has set a goal of producing more than 1/3 of the total 30,000 markers needed. In its first few months of operation, it has already made two public releases of data totalling 1598 human markers, as compared to 1782 markers included in the CEPH/Genethon map. The groups in the U.S. and France are working collaboratively to map more markers and assemble a reliable ordered set of yeast artificial chromosome clones, or YAC contig, of the entire genome. Other research groups working on individual chromosomes will incorporate the markers made by the whole genome groups into the high resolution maps they are constructing. These maps are needed for finding disease genes and for sequencing the genome.

HIGH COST OF GENOME TECHNOLOGY

Mr. Smith: The average cost of your research project grants, centers, and intramural dollar per FTE are among the highest at NIH. Why is research associated with the human genome so expensive?

Dr. Collins: The Human Genome Project is a highly interdisciplinary program with an emphasis on technology development. These interdisciplinary programs require the talents of engineers, physicists, chemists, computer scientists, mathematicians and others, working toward the common goals of developing highly effective systems for mapping and sequencing the human genome. These scientists are building the infrastructure that will not only assure completion of the Human Genome Project in a timely manner, but will also impact more generally on biological research and molecular medicine. An important task of the Human Genome Project is the development of fully integrated, modular, automated systems, especially for sequencing the human genome. The interdisciplinary nature of the research, the salary structure for highly skilled physical scientists, and the expense of engineering instruments and integrated systems, results in an increased cost per FTE in comparison with more traditional biological research.

NUMBER OF RESEARCH PROJECT GRANTS

Mr. Smith: From 1993 to 1995, your number of research project grants will drop by almost 30 percent, yet your budget allocates the same amount of funding to this mechanism in 1995 as in 1993. Why is there such a big decline in the number of grants supported?

Dr. Collins: FY 1993 was the last non-competing year for the initial grants funded in FY 1988. These grants were of a much smaller average cost than the awards funded subsequently. As the Human Genome Project has become more technologically-oriented, the costs of the research projects have increased dramatically. For example, during FY 1993 several very large sequencing grants were awarded. As NCHGR awards more DNA sequencing grants, a very expensive research effort, the average cost of grants will likely to continue to rise. The inevitable consequence, therefore, is a drop in the number of grants we can fund.

RESEARCH CENTERS

Mr. Smith: As you try to manage a tight budget and a growing intramural program, why are you choosing to add a $2.5 million research center in 1995?

Dr. Collins: The genome research centers play a vital role in accomplishing the goals of the Human Genome Program. In the current centers, the basic research findings and technology developments from the research grants program are translated into efficient, high throughput systems for the generation of data and production of maps. A significant amount of technology development is also taking place in these centers, particularly in the areas of automated instrumentation and informatics. In most of the centers now funded, work on genetic maps and physical maps is in full-production mode.

Attention therefore is now turning to the development of technology for DNA sequencing, particularly fully-integrated systems that will increase the speed and reduce the costs of all phases of the DNA sequencing process. Increasingly, this will demand effective collaboration among biologists, engineers, mathematicians, and computer scientists, among others. A center offers an excellent environment and support structure for such a multidisciplinary attack on the problem. Currently one of the NCHGR genome centers is working almost exclusively in the area of sequencing technology development. The additional center requested in FY 1995 will increase the NCHGR effort in this vital arena.

Mr. Smith: As you prepare to recompete the genome centers in 1995, have you revised their mission and scope of duties?

Dr. Collins: Considerable progress has already been made toward meeting the initial goals of the genome project. As a result, a new set of goals, extending beyond the original ones, was developed in 1993. Accordingly, the mission and scope of the genome centers will continue to evolve to reflect the new 5-year goals of the genome project. It is expected that the emphasis on genetic mapping will decrease; physical mapping efforts will turn toward achieving high resolution, annotation and closure of the maps; and increased effort will be devoted to the area of sequencing technology development, ramping up toward increased production of DNA sequence data.

RESEARCH TRAINING

Mr. Smith: You are the only NIH component that proposes a notable decrease in the number of research training grants in 1995. Your justification indicates that you do not expect the quality of the recompeting training grants to be high enough to maintain the same total number. Why is this the case? What steps do you plan to encourage training efforts in the genome field?

Dr. Collins: Genome science interfaces molecular biology with technology-related disciplines such as engineering, physics, computer sciences, mathematics and chemistry. The types of programs needed to train individuals in genomic sciences require institutions to develop entirely new approaches to training which include getting a new training program certified within the institution, developing new curricula, recruiting students with the appropriate educational background, and encouraging faculty in non-biology disciplines to collaborate in the training initiative. All of this requires tremendous time and effort on the part of the program directors. In a small new field such as genome science, there is not yet a pool of people large enough to provide a critical mass of training programs.

We are working with institutions to improve this situation, but also focusing on training of individuals through career awards and courses. Because these mechanisms are currently more successful, we have moved some training money into those categories.

We recently examined our research training needs for the next five years and plan to discuss the findings with our National Advisory Council at its May meeting. One of the proposed recommendations is that NCHGR staff identify institutions that have the capability to initiate interdisciplinary genomic sciences training programs and work with them in developing competitive applications. We also propose to streamline the application process and provide more flexibility in the training program by allowing short-term and pre- and post-doctoral training on the same grant. We plan to work with initial review committees so that they will have a better appreciation for genome sciences training programs.

One of the problems with recruiting individuals with the appropriate expertise into training programs is the stipend, which is not competitive with the customary career opportunities for such individuals. The NCHGR in 1992 established a Special Emphasis Research Career Award to attract non-biologists and this mechanism has proved very useful in recruiting individuals with the type of expertise needed for genome sciences. The advantage of this over the regular NRSA award is that it is a five year program and the salary ceiling is $50,000 compared to the maximum NRSA stipend of $32,300 and the usual 3-year limit for postdoctoral training. This program has been quite successful and we plan to increase the number of career awards in the future.

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS OF GENOMIC RESEARCH

Mr. Smith: Are you considering any modification of your ethics program to enhance its independence to make policy recommendations? Has the ethics program produced any recommendations to date, or only policy options to consider? Will the Department implement the Institute of Medicine recommendation to establish a national genetic testing advisory committee?

Dr. Collins: The ethics program for the U.S. Human Genome Project is designed to insure the independence of its activities and products. The research, education, and policy analysis projects that it supports are sponsored through extramural federal assistance grants, and its grantees have complete reporting independence from NIH or DOE. In addition, the NIH-DOE Ethical, Legal and Social Issues Working Group, which helps the agencies monitor and coordinate the programs activities, is also, as a group of external consultants to the NIH and DOE, free to make recommendations independent of federal clearance. We are, however, in the process of enhancing the capacity of that Working Group to develop and deliver policy recommendations, by expanding the staffing of the program to provide direct policy analysis and logistical support for the Group's activities.

The ethics program's approach has been, where possible, to commission policy studies from organizations and individuals that have the standing to be influential on particular issues, and allow them to make their policy recommendations independently of NIH or DOE. Under this approach, the program has already sponsored reports from authoritative bodies that make substantive recommendations for professional and public policy in each of the program's high priority areas, and numerous individual program grantees have offered recommendations on specific issues which have also become influential.

The following is a listing of recommendations developed by ELSI research:

I. ELSI-sponsored recommendations regarding the management of genetic information about individuals and families ("Genetic Privacy"):

A. Information Gathered For Research Purposes

American Association for the Advancement of Science, Ethical and Legal Issues in Pedigree Studies, 1993. [recommendations to researchers on the design of genetic studies involving families]

U.S. Office of Protection from Research Risk, Protecting Human Research Subjects: Institutional Review Board Guidebook; "Chapter H: Human Genetic Research." 1993. [recommendations to institutions on the review of genetic studies involving families]

Madison Powers, "Publication-related risks to privacy: ethical implications of pedigree studies," IRB: A Review of Human Subjects Research 15(1993): 7-11. [Influential grantee report with recommendations on publication practices in genetic research].

B. Information Gathered For Personal Identification Purposes

National Research Council, DNA Technology in Forensic Science, 1992. [Over 40 professional and public policy recommendations on the regulation and practice of DNA typing for personal identification]

C. Information Gathered For Clinical Purposes

National Academy of Sciences/Institute of Medicine, Assessing Genetic Risks: Implications for Health and Social Policy, 1994. [Professional and public policy recommendations on management of confidential clinical information.]

George Annas, "Privacy rules for DNA databanks," JAMA 270(1993): 2346-2350. [influential grantee report on standards for clinical information management].

II. ELSI-sponsored Recommendations regarding the fair use of genetic information outside the clinical setting ("genetic discrimination")

A. Information gathered for insurance underwriting purposes

NIH-DOE Task Force on Genetic Information and Insurance, Genetic Information and Health Insurance, 1993. [Public policy recommendations to prevent the discriminatory use of personal genetic information in health care coverage.]

B. Information gathered for employment decision-making purposes

NIH-DOE ELSI Working Group, "Statement on Genetic Discrimination and the Americans with Disabilities Act," 1991. [regulatory recommendations to prevent exclusionary genetic screening by employers]

Mark Rothstein, "Genetic discrimination in employment and the Americans with Disabilities Act," Houston Law Review 29(1992). [Particularly influential grantee report]

III. ELSI-sponsored recommendations regarding the responsible clinical introduction of new genetic tests ("genetic services")

NIH Workshop Report, "Population Screening for the CF gene," New England Journal of Medicine, 323 (1990): 70-71. [professional policy recommendations regarding the introduction of CF carrier testing]

NIH Workshop Statement, "Reproductive genetic testing: Impact on Women," American Journal of Human Genetics 51(1992): 1161-1163. [professional policy recommendations regarding reproductive genetic testing]

NCHGR/NCI Workshop Report, "Recommendations on Predictive Testing for Germ Line p53 Mutations Among Cancer-prone Individuals." Journal of the National Cancer Institute 84(1992): 1156-1160. [professional policy recommendations regarding genetic testing for cancer risk]

National Advisory Council for Human Genome Research and the ELSI Working Group, "Statement on Presymptomatic Testing for Cancer Risk," JAMA March 9, 1994. [professional policy recommendations regarding genetic testing for cancer risk]

Ben Wilfond and Kathleen Nolan, "National policy development for the clinical application of genetic diagnostic techniques," JAMA 270(1993): 2948-2854. [influential grantee report on genetic technology assessment].

We are not aware of any activity by the DHHS to establish a national genetic testing advisory committee. However, the NIH-DOE ELSI Working Group has established a Task Force on Genetic Testing, which will begin to address many of the issues that the Institute of Medicine would delegate to a national genetic testing advisory committee. The NIH-DOE Task Force will be composed of clinicians, health policy experts, consumers, and representatives from the relevant regulatory bodies and professional societies. Its mission will be to help articulate policy approaches to the regulation of new genetic testing techniques as they move from the research laboratory to the clinic. Dr. Neil Holtzman, Director of the Genetics Policy Studies program at the Johns Hopkins University School of Medicine, has been appointed Chair of this Task Force.

PATENTING OF GENE FRAGMENTS

Mr. Smith: Could you review the chronology of the issue of NIH seeking patents for gene fragments of unknown function and clarify the current NIH policy? Is it problematic if private industry continues to seek these patents?

Dr. Collins: On June 20, 1991 the NIH filed its first patent application with the U.S. Patent and Trademark Office claiming 315 cDNA sequences. A continuation-in-part (CIP) application and an additional application were filed in 1992, such that a total of 7,184 sequences were claimed. On August, 20, 1992, the PTO issued an initial Examiners Actions rejecting the claims in the original patent and its CIP. The NIH responded to the PTO's office action on February 19, 1993, and a final Examiner's office action rejecting the claims in the CIP application was issued by the PTO on August 10, 1993.

On February 11, 1994 the NIH announced that it would not appeal the rejection by the U.S. Patent and Trademark Office of its patent application on human cDNA sequences. Following extensive discussion with scientists and experts in patent law, the NIH concluded that it is not in the best public interest for NIH to pursue patents on sequences of unknown practical utility in that these sequences are primarily useful as research tools and not as commercial products.

Issues relating to patenting of sequences of unknown function are complex and there are differing opinions in the industrial sector. A number of companies are continuing to pursue such patents. Continued public dialogue on this subject is desirable and the NIH will participate in and/or facilitate this process. These discussions would likely include representatives of industry and the international community.

Mr. Smith: The 97 percent of the genome that does not encode proteins has been variously described as "junk DNA" with no purpose and a complex mix of DNA with important functions. Which side of the argument do you come down on? If "junk DNA" turns out to be important, will it require a genome project to decipher? Would this be a massive enterprise given the share of the genome that "junk DNA" comprises?

Dr. Collins: The human genome carries numerous types of sequences that in sum provide the genetic basis for human development and function. Recent findings support the notion that among the non-protein encoding sequences are those that are key to understanding the molecular basis of disease, gene regulation, and inheritance and maintenance of the genome.

For example, some sequences previously labeled "junk," such as satellite DNA, are now thought to be indispensable for chromosome survival. Other non-protein encoding sequences are now associated with genetic diseases. Indeed, these new insights into the functions of "junk" sequences have led researchers to express the notion that the genome is a complex "information organelle" with highly sophisticated mechanisms for systems integration.

The only way that we will know what the non-coding sequences are doing will be to sequence the entire DNA and see what they look like. I am confident that we will learn many intriguing and unexpected things from examining the full DNA sequence and that our understanding of the functioning of cells will be enormously enriched as a result. While much will become apparent when the DNA sequence is examined, it is likely that a full understanding of all the complexities built into the genome will take many years beyond the completion of the genome project to achieve. Most likely such studies will be pursued under traditional investigator-initiated research grants.

NCHGR INTRAMURAL PROGRAM

Mr. Smith: Identify the beginning- and end-of-year on-board strength for the intramural program 1993-1995.

Dr. Collins: The estimated on-board strength, FTE positions filled, for the NCHGR Division of Intramural Research is as follows:

	FY 1993	FY 1994	FY 1995
Beginning-of-Year:	0	38	132
End-of-Year:	38	132	156

The FY 1994 level assumes the lifting of the PHS hiring freeze.

Mr. Smith: Where are your intramural laboratories located, and how many are there?

Dr. Collins: The Division of Intramural Research, National Center for Human Genome Research is located in Building 49, on the NIH campus in Bethesda, Maryland. It has three laboratories, the Laboratory of Cancer Genetics, the Laboratory of Genetic Disease Research, and the Laboratory of Gene Transfer. In addition there are three branches within the Intramural Program, the Diagnostic Development Branch, the Medical Genetics Branch, and the Clinical Gene Therapy Branch.

Mr. Smith: What are your 1996-1999 cost and FTE projections for the intramural program?

Dr. Collins: The NCHGR Division of Intramural Research expects to reach a steady state by the end of FY 1995. After FY 1995, NCHGR expects increases only to keep abreast of inflation or take advantage of dramatic, unanticipated opportunities.

Mr. Smith: How many of the intramural staff have come from the University of Michigan?

Dr. Collins: The NCHGR has hired 20 individuals who were formerly employees of the University of Michigan. In addition, 12 trainees have come with these scientists to complete their training at the NCHGR.

Mr. Smith: What share of the Director's time is devoted to conducting science in the intramural lab?

Dr. Collins: I spend about 30 percent of my time on research in my laboratory in the intramural program of NCHGR.

FUNDING FOR THE U.S. HUMAN GENOME PROJECT

Mr. Smith: Identify 1991-1995 Department of Energy and NIH spending on the Human Genome Project.

Dr. Collins: The budget for the Department of Energy and the NIH for the Human Genome Project follows:

The Budget for the Human Genome Project
(Dollars in millions)

	1990 Act.	1991 Act.	1992 Act.	1993 Act.	1994 Est.	1995 Request
NIH*	59.5	87.4	104.8	106.1	107.7	112.6
DOE**	27.2	47.4	61.4	64.5	68.0	73.9
Total	86.7	134.8	166.2	170.6	175.7	186.5
Five Year Plan		135.1	169.2	218.9	246.8	259.9

* Excludes the Division of Intramural Research
** DOE figures do not include salaries and expenses of DOE employees devoted to this effort.

RESEARCH CENTERS

Mr. Smith: Identify the number, type and subject areas of research centers supported in 1994.

Dr. Collins: The "centers" line represents a mixture of four different types of centers. In the portfolio for FY 1994 are six specialized centers focusing on: the physical and genetic maps of human chromosome 4; the physical maps of human chromosomes 7 and X; the physical and genetic maps of human chromosome 22; the genetic map of the human genome; the physical and genetic maps of the mouse genome and the physical map of the human genome; and the physical map of the Drosophila genome and DNA sequencing of large regions of this genome.

There are also three core centers focusing on: mapping and sequencing technology and the physical maps of human chromosomes 17 and X and the genetic map of human chromosome 6; mapping and sequencing technology to increase the efficiency and decrease the time required to map and isolate a disease gene, using the breast cancer gene as a model; and mapping and sequencing technology, new informatics tools, and mapping disease genes.

In addition, there is one exploratory center focussing on technology development for DNA sequencing (DNA chips for sequencing by hybridization), and one biotechnology resource center to establish and maintain a Drosophila melanogaster (fruitfly) database. Thus, eleven centers are currently funded, with two more anticipated by the end of the fiscal year.

RESEARCH TRAINING

Mr. Porter: Your congressional justification shows a reduction of 45 full-time training positions in FY 1995. Will you explain the reason for this decline?

Dr. Collins: The NCHGR expects approximately 92 percent of the training positions to turn over in FY 1995. Because genome science interfaces molecular biology with technology-related disciplines such as engineering, physics, computer sciences, mathematics and chemistry, the type of programs needed to train individuals in genomic sciences require institutions to develop entirely new approaches to training. This includes getting a new training program certified within the institution, developing new curricula, recruiting students with the appropriate educational background, and encouraging faculty in non-biology disciplines to collaborate in the training initiative. All of this requires tremendous time and effort on the part of the program directors. In a small new field such as genome science, there is not yet a pool of people large enough to provide a critical mass of training programs. Therefore, we do not expect to get many competitive applications for training grants.

We are working with institutions to improve this situation, but also focusing on training of individuals through fellowships, career awards, and courses. Because these mechanisms are currently more successful, we have moved some training money into those categories.

HUMAN TISSUE FOR GENE TRANSPLANT THERAPY

Mr. Porter: Human tissues are now needed for "gene transplant therapy" research, a new area of science now rapidly emerging. Are you enlarging support for human tissue and organ retrieval through the National Disease Research Interchange in this particular area?

Dr. Collins: The National Center for Human Genome Research conducts gene therapy research, but this research does not require tissue or organ banks. We have therefore not supported the National Disease Research Interchange. It is, however, supported by the National Center for Research Resources, the organization charged with supporting resources of NIH-wide significance.

GENE DISCOVERIES HELPED BY HUMAN GENOME PROJECT

Mr. Porter: I was very interested to read the January article in Time Magazine about genetics and the Genome program. It seems that new disease genes are being discovered with fair regularity. What role has the Human Genome Project played in these discoveries?

Dr. Collins: One of the overall goals of the Human Genome Project is to provide the infrastructure (materials, tools and information) for scientists to identify disease genes. Progress on the Human Genome Project has helped to accelerate the pace at which disease genes are being identified through advances in several different avenues of genome research. The human genetic linkage map, which consists of markers along the chromosome that help researchers home in on the region where a disease gene is located, is now of sufficient detail that the time required to locate a gene has been reduced, in many cases, from years to months. The localization of many disease genes, including Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease), familial Colon Cancer and Spinocerebellar Ataxia was expedited by the availability of the wealth of markers on the human genetic map.

Once a gene has been localized to a specific chromosomal region, it then has to be isolated. NCHGR supports the development of several different approaches to the efficient identification of genes within a localized stretch of DNA. One of the best examples of the power of these approaches was demonstrated in the identification of the gene for Huntington's Disease. This gene was cloned 10 years after it had been genetically mapped by exploiting one of these newly developed techniques to identify genes within a defined chromosomal region. The isolation of the gene for Spinocerebellar Ataxia (SCA1) was facilitated by the discovery of unusual repeated sequences found in a number of disease genes through work that was partially funded by NCHGR.

The search for the genes responsible for both Amyotrophic Lateral Sclerosis and Multiple Endocrine Neoplasia, type 2 was greatly expedited by the existence of candidate genes already mapped to the disease gene regions identified by genetic linkage mapping. However, only a small fraction of the estimated 50,000 to 100,000 genes have been identified and mapped to date. Improved technology for gene identification and for the placement of genes onto the physical map of the human genome will greatly increase the rate at which disease genes are identified. The following table lists inherited disease genes identified by positional cloning.

INHERITED DISEASE GENES IDENTIFIED BY POSITIONAL CLONING

Year	Disease	Year	Disease
1986	Chronic granulomatous disease	1993	Menkes' disease
	Duchenne muscular dystrophy		X-linked agammaglobulinemia
	Retinoblastoma		Glycerol kinase deficiency
1989	Cystic fibrosis		Adrenoleukodystrophy
1990	Wilms' tumor		Neurofibromatosis type 2
	Neurofibromatosis type 1		Huntington's disease
	Testis-determining factor		Multiple endocrine neoplasia type 2A
	Choroideremia		Von Hippel-Lindau disease
1991	Fragile X syndrome		Spinocerebellar ataxia I
	Familial polyposis coli		Wilson's disease
	X-linked Kallmann syndrome		Hereditary non-polyposis colon cancer
	Aniridia		Tuberous sclerosis
1992	Myotonic dystrophy		Lissencephaly
	Lowe syndrome		
	Norrie syndrome		

GENE THERAPY

Mr. Porter: Dr. Collins, you were quoted on the front page of the Washington Post on April 1st regarding the promise of gene therapy. How close are we to having effective, long-term gene therapy?

Dr. Collins: Gene therapy has great promise as a treatment for many different diseases. We have only just begun the research necessary to convert this potential to reality for most conditions. A few diseases are good candidates for treatment with the technology that we have available today, but effective treatment for most diseases awaits further progress. Each disease must be thought of as a separate problem to be solved. The initial patients given gene therapy, the two girls with severe immune deficiency, are doing very well and it is probable that the treatment as developed for that rare disease can be called effective. In addition, there have been very encouraging early results in gene therapy trials for diseases ranging from hypercholesterolemia to brain cancer. Since the entire experience with these treatments is so brief (the first treatment ever given was in September 1990), it would be premature to claim unequivocal success in any application so far tried.

An implication from the way your question is worded, is that gene therapy might only be successful if it is used for long-term applications. In fact, some of the most exciting potential uses of gene therapy are for short-term applications. For example, NCHGR and NINDS scientists are using gene insertion to modify brain cancers so that they are more easily killed by drug treatment. In this case, gene therapy which gives only a few days of gene expression is enough because it is being used as a kind of "molecular surgery."

While the exact strategies applied by gene therapists are in a state of rapid flux, it is likely that this powerful new approach to medical therapeutics will find its way into mainstream medical practice in another 10 to 15 years.

PROGRESS OF THE HUMAN GENOME PROJECT

Mr. Stokes: Can you bring us up-to-date on the progress made thus far in mapping and sequencing the human genome. Are we on target with the goal, explain.

Dr. Collins: Scientific progress on the Human Genome Project has proceeded at a remarkable pace and the project is currently on schedule. A first-generation genetic map is essentially complete, nearly two years ahead of the expected completion date. The improved quality of this map has reduced the time required to map a gene from a period of years to a matter of months in many cases. Efforts have turned toward improvements that will make the map more useful and accessible, with the anticipation that the time necessary to map a gene might be further reduced to a matter of weeks.

Progress in construction of the physical map, the other major type of genomic map being developed, has also been very rapid. A physical map of the human genome, with some regions mapped in more detail than others, is expected to be available in the next two to three years and a highly detailed map is expected within five years.

This progress has been achieved by focusing efforts on mapping as the essential early phase of the Human Genome Project. As the budget for the U.S. program has not reached the level originally recommended by the NIH-DOE advisors, this has meant that relatively less has been invested in the area of DNA sequencing during this period. This is not to say that steady significant progress has not been made in technology development for DNA sequencing: recently a U.S.-U.K. collaborative team announced the sequencing of a 2.2 million base pair region of DNA, exemplifying approximately a ten-fold increase in sequencing capability since the start of the Human Genome Project.

However, in spite of such progress, the current rate of advance in sequencing technology is far from sufficient to be confident that the complete sequencing of human DNA will be finished by the year 2005 at the originally projected cost. Although the goal of sequencing DNA at a cost of $0.50 per base pair may be met by 1995, or soon thereafter, the rate at which DNA can be sequenced currently will not be sufficient for sequencing the whole human genome. Overall sequencing capacity will have to double annually for at least the next 8 years if that task is to be successfully completed by 2005. Achieving this rate of increase will be a formidable task that will require a greatly enhanced technology development effort, as well as a larger number of research groups working in this area. Therefore, additional investment in new sequencing technologies is of the very highest priority.

INTRAMURAL PROGRAM

Mr. Stokes: More and more, the NIH is asked to justify the need for an intramural research program. What is NIH's plan for the Center's intramural program?

Dr. Collins: The NCHGR Intramural Research Program was established in February 1993 to provide a focus at the NIH for medical genetics research. I was appointed as Director of the NCHGR in April 1993 and recruitment for the Division of Intramural Research began shortly after that.

Three Laboratories (Genetic Disease Research, Cancer Genetics, and Gene Transfer) and three Branches (Diagnostic Development, Medical Genetics, and Clinical Gene Therapy) have been established and Chiefs have been recruited. Top level, renowned senior scientists have been appointed in this Program and research is already underway in each of these areas.

The NCHGR's Intramural Program includes core facilities accessible to other Institutes and new programs for visiting scientists and trainees, as well as programs in medical genetics and genetic counselor training.

It was essential to establish a critical mass: this facilitated recruitment of highest quality scientists, rapid program development, and economy of resource use. In no other way could the rich continuum from basic research to gene therapy with interdisciplinary exchanges of ideas be established.

After a two year ramp-up (FY 1994 and 1995) it is expected that the size of the NCHGR intramural program will plateau, with further increases only to keep abreast of inflation or take advantage of dramatic, unanticipated opportunities.

ETHICAL ISSUES IN GENOMIC RESEARCH

Mr. Stokes: The ethical and legal issues surrounding human genome research remains. Have we gotten any better at addressing these concerns?

Dr. Collins: The NCHGR's program on ethical and social issues is a pathbreaking experiment for the NIH, aimed at anticipating societal problems before they arise and developing safeguards that allow us to reap the benefits of new advances in genetics while minimizing possible adverse effects. Since there is no precedent for this kind of program, we must learn as we go how best to accomplish our goals. I believe the ELSI program has made an excellent start and is now poised to make solid contributions towards addressing these issues.

Since 1990, the activities of the NCHGR's ELSI Branch have set precedents, generated information, and provided models that have improved our ability as a society to address the ethical and legal issues raised by new advances in human genetics. The program is also evolving, to be able to capitalize on these new abilities.

The first important way in which the NCHGR has helped improve our ability to address these issues has been by helping to establish the importance of prospective, patient-centered, impact studies of new genetic tests prior to their widespread clinical use. This precedent was set by the NCHGR's commitment to pioneering pilot studies of testing and counseling for cystic fibrosis mutations in 1991, and has subsequently been endorsed and emulated by the research communities seeking genetic factors in heart disease and cancer, and praised as "evidentiary" health policy development by the health policy community. This year, the NCHGR has launched a major collaborative effort with the National Cancer Institute to apply its prospective technology assessment approach to genetic testing for cancer risks.

The second way the activities of the ELSI program have improved our policy-making capacities has been by raising public awareness of the issues and supplying policy-makers with the basic information they need to develop sound, well informed responses. There are several indirect measures that indicate that the program's educational and research activities are bearing fruit: For example, in 1990 only three states (CA, NY, RI) considered legislative proposals to combat the discriminatory use of personal genetic information. Today, legislatures in at least 17 states are considering measures to protect individual autonomy in genetic testing and confidentiality of the test results, and to prevent genetic discrimination. Similarly, current surveys of professional knowledge and attitudes regarding genetic issues compare quite favorably with surveys conducted before 1990 in terms of professional awareness and sensitivity to issues.

Even the presentation of genetics issues in the public media is a good measure of the extent to which our program's message is getting through. Before 1990, studies show that media reports were polarized as either inappropriate glorifications or vilification of genetic science. Since 1990, reports on new advances have shown a shift away from both extremes, to balanced presentations of the promises and risks of the new knowledge.

The NCHGR ELSI program has also produced direct aids to the resolution of these issues, by sponsoring and supporting policy analyses and recommendations on particular issues by organizations in positions to influence professional practice and public policy-making. Thus, the 1992 report by the National Research Council on standards for forensic DNA typing, the 1993 guidance for genetic researchers from the HHS Office for Protection from Research Risks, the 1993 NIH-DOE report on genetic information and health insurance, and the 1994 report on clinical standards in genetic services by the National Academy of Sciences all offer options to policy-makers and the professions for addressing the most urgent genetics-related issues.

Finally, in order to capitalize on the resources it has produced, the NCHGR is in the process of expanding the activities of its ELSI program to allow it to help coordinate and facilitate the development of practical responses to these issues. In addition to the extramural research and education program, the NCHGR plans to add a policy analysis unit within its intramural program to assist the NIH-DOE Ethical, Legal and Social Issues Working Group monitor and report on the policy recommendations emerging from its work. This will allow the NIH-DOE Working Group to expand its activities, by establishing a number of Task Forces for produce reports on urgent issues. Current high priority initiatives for the Working Group include the regulation of commercial DNA diagnostic services, the prevention of genetic discrimination in health care coverage, and the development of adequate privacy protections for personal genetic information held by researchers, clinicians, and public health officials.

HIGH PERFORMANCE COMPUTING

Mr. Stokes: The NIH FY 1995 budget request includes $81.8 million, or a $24 million increase, for high performance computing. How will the major initiatives under the purview of the Center benefit from this investment?

Dr. Collins: The Human Genome Project (HGP) will benefit in numerous ways from the investment in High Performance Computing and Communications. Some specific examples include:

- The NLM Medical Connections Program will provide "jump start" funds to academic medical centers and health care organizations to allow them to connect to the National Research and Education Network (NREN). This will allow researchers and clinicians at these institutions to access the rapidly growing databases of information produced by the HGP.
- The NLM Biotechnology Informatics program supports the National Center for Biotechnology Information which manages the GenBank database of nucleic acid sequences. This is the most important repository for the gene sequences determined by HGP researchers and is an essential means of making the results of the HGP available to biomedical researchers.
- NLM HPCC Training Grants will train biomedical professionals in informatics and will train computer and information scientists in the application of these technologies to health problems. Because the HGP is a data-driven project, an increased number of cross-trained informatics professionals will be essential to economically managing the large amount of data produced. At present there is a significant shortage of these professionals.
- The NCRR Advanced Software Technology and Algorithms program will support the development of advanced algorithms for comparing genetic sequences, an essential first step in determining the functions of the human genome.
- The goal of the DCRT High Performance Biomedical Computing Program is to make high performance computing and communications available to NIH intramural staff, including the intramural investigators of the NCHGR. Under this program DCRT is developing a number of advanced computational methods that will be of particular value to NCHGR researchers, particularly methods for genetic sequence comparison and human genetic linkage analysis.
- The NCI Frederick Biomedical Supercomputing Center provides high performance computing to the entire biomedical scientific community. Specific capabilities of value to the HGP include structure prediction of nucleic acids, genomic sequence analysis, and linkage analysis.

HISTORICALLY BLACK COLLEGES AND UNIVERSITIES (HBCU)

Mr. Stokes: What are some of the major initiatives underway at the Center to increase the participation of historically black colleges and universities in biomedical research?

Dr. Collins: The Center is focussing its efforts on providing opportunities for students and faculty to develop the capacity to pursue genomic research. Although the Center uses all the NIH mechanisms, we find the minority supplement and minority travel award well suited as a means of introducing students and faculty members to genomic sciences. The minority travel award has been used to support students and faculty members to attend workshops, meetings, and courses as well as to provide research experiences and didactic training through visits to genome laboratories. The minority supplement has been used to support those who wish to pursue a research project. The NCHGR's intramural program was recently established and as part of its outreach activities, the Visitor's laboratory will bring to the NIH campus minority researchers interested in learning the latest techniques in genomic research. Because there is a rather small community interested in genomic research, the Center's staff can work with individual faculty to help them develop appropriate projects for funding.

PREVENTION AND HEALTH CARE REFORM

Mr. Stokes: With health care reform on the horizon, there is increased interest in and value placed on health promotion and disease prevention. What are some of the most significant initiatives in prevention research underway at the center?

Dr. Collins: The Human Genome Project is providing researchers with the tools to rapidly and efficiently search for disease genes. The discovery of genes that lead to a predisposition to specific diseases can permit the identification of individuals who have a high risk for these diseases. The identification of such individuals allows for increased surveillance and early treatment, and for the application of early interventions aimed at disease prevention.

Gene discovery will allow health care providers to diagnose and treat patients more directly and efficiently by altering the course of the disease before it becomes advanced. The ability to identify individual genetic risks for future disease will allow the design of individualized preventive medicine strategies focused on life-style alterations and medical surveillance to keep people well.

Early detection is particularly important for the successful treatment of human cancers. Breast cancer and colon cancer are two examples of common catastrophic diseases that cause serious illness and a significant number of deaths. Because effective treatments are available for these diseases when diagnosed in the early stages, prognosis is greatly improved by early detection. Using an array of gene-finding tools developed by the Human Genome Project, an international team of scientists recently located genes that lead to colon cancer in approximately 1 to 200 people in the western world. In other research supported in part by the NCHGR, researchers have tracked a breast cancer gene to a particular region on chromosome 17 and will likely isolate the gene in the near future. Discovery of these genes will pave the way for diagnostic tests which can identify individuals who are at increased risk for developing these diseases. Increased surveillance and early detection should be able to decrease the number of deaths from colon or breast cancer among individuals who carry these genes.

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research area under the purview of your center.

Dr. Collins: In addition to molecular biologists, the human genome program needs engineers, chemists, physicists, computer scientists and mathematicians who, in order to be successful, must understand the technical obstacles to getting the job done as well as the biology. The greatest challenge is to attract, train and retain such individuals into molecular biology programs. This is very difficult primarily because stipends on training programs are not competitive with other career opportunities such individuals have. The career path for such interdisciplinary scientists, especially in academia, is also problematic at the present time. The NIH does a good job of training biological scientists. This model, however, does not work as well for non-biologists. Therefore, NIH must develop a different approach to training individuals in these non-traditional research disciplines and universities must recognize the importance of such individuals in research as it will be practiced in the 21st century.

MINORITY RESEARCH AND TRAINING

Mr. Stokes: Please describe the measures the Center takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Collins: The Center's research program is not focussed on any specific disease. Our mission is to develop tools that will help other scientists who are working on disease-oriented research projects to identify and isolate their gene(s) of interest more quickly and inexpensively. To the extent that we are successful in these efforts, we will be successful in helping researchers who are studying diseases and disorders that affect minorities disproportionately. Thus, we support minority faculty members who are developing maps of chromosomal regions and DNA sequencing technology. We provide support for minority students to get doctoral or combined doctoral/medical degrees and for the training of faculty members so that they can eventually pursue genomic research. We also support high school and college students to participate in research projects during the summer and throughout the school year. Our intramural educational program is in the process of developing an outreach program to inform the minority community about the human genome program.

MINORITY EMPLOYMENT AT NCHGR

Mr. Stokes: How many GS-15 and above positions are there in your institute? How many employees in your institute are in GS-15 and above positions? In your institute, currently, how many African Americans are at the GS-15 and above level? In what position are they? In your institute how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze. If so, what was the response? If the freeze were lifted, how would it help the EEO problem in your institute?

Dr. Collins: The NCHGR currently has 19 positions at GS-15 and above. Sixteen of the positions are occupied, one by an African American. This individual is the Chief, Mapping Technology Branch, Division of Extramural Research. The NCHGR currently has no exceptions for African Americans to be appointed or promoted to GS-15 and above. NIH has requested relief from the Public Health Service (PHS) hiring freeze imposed in September 1993 because the NIH had successfully managed its FTE ceiling. The request is under consideration by PHS. Operating under the freeze curtails our ability to target minorities currently outside the PHS and severely limits the pool of applicants for positions.

SUPPORT TO MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by the Center?

Dr. Collins: For fiscal year 1994, the Center's support for minority programs is approximately $624,000; $269,000 of this goes to support research projects in minority institutions.

HBCU PARTICIPATION IN THE HUMAN GENOME PROJECT

Mr. Stokes: Minority institutions seem to face a "Catch 22" situation. They are often told that they cannot get funding because they do not often have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Center's programs and activities?

Dr. Collins: The Center has been very successful in working with HBCU institutions that are recipients of the National Center for Research Resources' Research Centers in Minority Institutions (RCMI) Awards. For example, we supported one faculty member from Clark Atlanta University to attend a course at the Cold Spring Harbor Laboratory to learn new mapping techniques. He then arranged to spend several weeks in a research intensive genome center laboratory. Following this experience, the faculty member applied to the Center for a three-year grant which was funded. The initial review group suggested that in order for the research to be pursued, 50 percent effort was required rather than the 25 percent effort requested. With approval from his university, the faculty member was given the additional release time. In addition, the award included funds for him to make annual visits to genome laboratories to learn new techniques.

MINORITY TRAINING PROGRAMS

Mr. Stokes: Explain the proposed funding for the programs of your Center that are designed to increase the participation of underrepresented minorities in biomedical research, and research training?

Dr. Collins: The Center has found the entire range of mechanisms targeted to minorities to be useful and will continue to use them to attract minority students and faculty into genomic research. Most notable is the individual pre-doctoral minority program which has been particularly successful in identifying future scientists and clinician scientists for biomedical research. We are committed to funding every reasonable application submitted to us and to work with applicants to improve their skills as needed.

NATIONAL CENTER FOR RESEARCH RESOURCES

NCRR ACTION PLAN

Mr. Smith: You have developed a strategic plan for the Center -- the first in its history. How has it changed the way you do business and construct your budget?

Dr. Vaitukaitis: The NCRR Strategic Plan has been instrumental in providing the NCRR with a clear vision of the future basic and clinical research trends and the resources needed by investigators to facilitate research and to convert scientific ideas into the reality of better health for our Nation's citizens. NCRR is planning several new initiatives in response to this Plan. Some examples are:

In the area of Clinical Research, the Plan identified the "need to establish gene therapy resources." NCRR is responding with a Request for Applications (RFA) for FY 1995 for a Human Applications Laboratory to be funded by NCRR in collaboration with a number of other NIH Institutes and Centers.

In the area of Critical Technologies, the Plan identified the need to "promote innovative research to bridge the gaps between basic research, bioengineering and clinical research." The NCRR is responding with an RFA in FY 1995 for new bioengineering approaches to disease prevention and control as well as to decrease health care costs.

In the area of Research Models, the Plan identified the need "to establish national genetic resources for research models." The NCRR is responding in FY 1995 with an RFA for a second "National Resource for Transgenic Animals" in new animal species, such as transgenic rats and rabbits, and to expand existing resources for induced mutants.

In the area of Human Resources, the Plan identified the need to "promote science literacy and the public understanding of science." In response, the NCRR plans to modify support and dissemination of existing science education programs as well as other model programs. The target audience for this initiative includes students in grades K-12, girls and minority students and the public.

HIGH PERFORMANCE COMPUTING

Mr. Smith: Describe for us the nature of your Center's role in the High Performance Computing and Communications initiative as compared to that of the National Library of Medicine.

How much funding is included for the high performance computing initiative in your 1995 request?

Dr. Vaitukaitis: The roles of the NCRR and the National Library of Medicine (NLM) in the High Performance Computing and Communication initiative are complementary rather than overlapping. NCRR supports research and development of innovative algorithms and software for use by the biomedical research community to address grand challenge research problems such as complex biological system simulations, protein structure analysis, structure-based drug design, and multimodal, real-time biomedical imaging. The NLM focus is on informational resources and applications of telemedicine. It is anticipated that NCRR developments in areas like real time imaging and virtual reality will provide the underpinnings for future NLM telemedicine activities.

The FY 1995 NCRR request is $6.8 million above the level for FY 1994, for a total of $22.6 million.

GENE THERAPY

Mr. Smith: Tell us more about the regional gene therapy labs you are developing as a shared resource for researchers. Why are they needed?

What will be the extent of your Center's involvement?

Will other NIH institutes also participate?

What is the projected annual cost of these regional centers?

Dr. Vaitukaitis: Gene therapy is a new therapeutic approach in molecular medicine for the treatment of many inherited and acquired disorders. To date, gene therapy has been used to treat patients with familial hypercholesterolemia, cystic fibrosis, selected cancers and immunologic diseases. It is expected that within the next few years, gene therapy may be extended to the treatment of blood disorders (sickle cell anemia, hemoglobinopathies), hypertension, heart and pulmonary diseases. In particular, this form of treatment promises success for rare inherited disorders such as Gaucher's disease, adenosine deaminase deficiency and others where successful treatment would lead toward restoration of normal health.

One of the recognized barriers for scientists working in this area is the inability to obtain funding for the production, safety testing and distribution of the vectors which carry the genes to the human host. Funding is available for gene identification, vector development, initial tissue culture and animal studies and the final step of patient treatment which can occur in the General Clinical Research Centers. Because of the cost for vector production, it is not feasible for each investigator or university to build suitable facilities to house this vital link for gene therapy vectors.

To facilitate this function, the National Center for Research Resources is working together with the National Cancer Institute; National Institute of Diabetes, Digestive and Kidney Diseases; National Institute of Allergy and Infectious Disease; National Heart, Lung and Blood Institute; and the National Center for Human Genome Research to establish Regional Vector Laboratories. The total funds to be set aside for this purpose and the specific contributions of each Institute and Center have not yet been finalized but we estimate that between $3 to $5 million will be required for this effort in FY 1995.

EXTRAMURAL CONSTRUCTION

Mr. Smith: How many applications have you received for research facility construction and renovation in 1994?

How do you intend to allocate these funds, and what is expected to be the average grant size?

Dr. Vaitukaitis: To date 69 applications have been received in response to the Request for Applications for research facility construction and renovation grants in FY 1994.

The applications are to be peer reviewed in June, and will undergo a second level of review by the National Advisory Research Resources Council in September. Four to ten grants will be awarded in September. The allocation of funds depends upon the applicant institution meeting requirements for matching funds and other administrative criteria specified in the application, but the primary factor in funding will be the recommendations from the peer review groups on the relative merit of the applications.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Smith: How many beds are supported by your General Clinical Research Centers (GCRCs)?

What is the average occupancy rate?

How many square feet of space do the GCRCs occupy overall?

What share of GCRC research is done on an outpatient versus inpatient basis?

For the record, can you compare these figures to the clinical center on the NIH campus?

Dr. Vaitukaitis: The GCRC program does not support a specific number of research beds. Some GCRCs are funded with a "discrete" configuration for which a fixed number of beds are supported, if that funding approach is cost-effective. Other centers are funded by the "per diem" method, which pays for actual number of research bed days used. At some GCRC sites both methods may be used to accommodate off-site (scatter beds) for clinical research in specialized units such as a neonatal intensive care unit, a coronary intensive care unit, or a psychiatric unit.

In "discrete" Centers, occupancy is kept high by admitting category B, C and D patients which provide "service patient credits," which decrease the cost of operating those centers. Through these mechanisms, the GCRCs have been very cost effective, with very efficient utilization of not only the beds, but also GCRC-supported paramedical personnel. The utilization of each GCRC is closely monitored by NCRR staff and the approved level of research bed days is issued each year based on previous and anticipated utilization.

An example of a discrete GCRC is the University of Utah General Clinical Research Center. In the University Hospital, the GCRC occupies 3,011 square feet of space, including inpatient and outpatient rooms, waiting and reception areas, utility room, and nurses station. In an adjoining wing of the medical school, the GCRC occupies another 2,894 square feet of space including offices and Core Laboratories (separate rooms for radioimmunoassays, virus transformation, chromatography, and sample processing). In addition, scatter-beds in the neonatal intensive care unit are used.

In FY 1982, there were 117,150 total outpatient research visits as compared to 153,322 total inpatient research days. Ten years later, in FY 1992, there were 203,323 outpatient research visits (an increase of 74%) compared to 85,288 total inpatient research days (a 44% decrease). Thus, in FY 1992, there were approximately 2.4 times more outpatient visits than inpatient days. This increased trend in research outpatient utilization is expected to continue.

In FY 1992, there were 85,288 inpatient research days in the GCRCs, and 87,521 in the NIH Clinical Center. There were 203,323 outpatient research visits in the GCRCs, and 85,992 for the NIH Clinical Center.

COMPETING RESEARCH PROJECT GRANTS

Mr. Smith: Why is the cost of your new grants in 1995 projected to increase by almost 7 percent, well above the biomedical research deflator?

Dr. Vaitukaitis: The growth in the average cost of competing grants from FY 1994 to FY 1995 exceeds the Biomedical Research and Development Price Index for NCRR because of the change in mix in the types of grants and the science funded. The NCRR expects to fund more Phase II Small Business Innovative Research grants and to increase the number of large program project grants funded. In addition, new high performance computing and communications grants will be more expensive than the average grant supported in FY 1994.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Smith: How many years have the current Research Centers for Minority Institutions (RCMI) received these special grants? How many more years do you expect they will need this assistance?

Dr. Vaitukaitis: The RCMI Program was initiated in FY 1985. Seven awards were made the first year, eight in FY 1986, two in FY 1988, one in FY 1992 and one in FY 1993. Because of the differential in the time that the institutions have received support from the RCMI Program, and the different infrastructure needs among the eligible institutions, plans are now underway to evaluate the RCMI Program in terms of accomplishing its goals and the mechanisms used by the participating institutions. A key part of this evaluation will be an assessment of infrastructure needs of the institutions, as well as the future direction of the Program. To date, the RCMI Program support has been provided for the development of the basic science needs in specific departments. A new direction for the RCMI Program will be the development of clinical research infrastructure at the eight RCMI grantee institutions with affiliated medical schools in order to facilitate the participation of these institutions in clinical research. This will also increase the participation of minorities in clinical research, including clinical trials.

Mr. Smith: What is the infrastructure initiative for RCMIs that you describe in your budget justification?

Dr. Vaitukaitis: The Research Centers in Minority Institutions (RCMI) Program has developed an initiative to enhance the capability for clinical research in the health sciences. The RCMI program will implement this through competitive grant support to eligible predominantly minority institutions that offer the doctorate in the health professions and/or health related sciences. The ultimate goal of this initiative is to increase the number of independent clinical investigators at predominantly minority health professional schools and graduate institutions to conduct clinical research, to increase clinical research on those diseases and disorders which disproportionately impact underrepresented groups and to increase the number of minorities participating as clinical research subjects.

NCRR VACANCIES

Mr. Smith: According to the organizational chart in our justification, a number of your offices have leadership vacancies. What progress are you making in filling these slots?

Are you undertaking a broader reorganization of your Center?

Dr. Vaitukaitis: We have five leadership vacancies within the NCRR. Filling the position of Deputy Director will begin the overall leadership change within NCRR and I anticipate that that position will be filled in the near future. Recruitment for the other positions will be undertaken in the near future with National searches.

We have recently completed our first formal planning activity for NCRR, the result of which is the NCRR Strategic Plan: "A Catalyst for Discovery." As we begin to implement that plan, some reorganizing within NCRR will occur. Moreover, decreasing the number of Federal employees will require streamlining and coalescing of management and supervisory functions wherever possible.

The National Institutes of Health (NIH) has recently reviewed its entire listing of Senior Executive Service and comparable positions. As soon as NIH completes its review and allocates positions to NCRR, we will begin recruiting for other senior level vacancies.

BIOMEDICAL RESEARCH SUPPORT

Mr. Smith: Is there any specific statutory authority for biomedical research support grants? If funds were provided, could you award these grants for any purpose you chose and through any funding mechanisms?

Dr. Vaitukaitis: Biomedical Research Support Grants (BRSG) are authorized under the Public Health Service Act, Section 301; Public Law 86-798; and 42 U.S.C. 241.

In the past the wide statutory authority has been used to create many new programs including the Health Sciences Advancement Award, the Biomedical Research Development Award, the Minority

Biomedical Research Support Program, and the Shared Instrumentation Grant Program. These new funding mechanisms were designed to broaden and enhance the scope of biomedical/behavioral research.

FUNDING FOR NCRR PROGRAMS

Mr. Smith: Identify 1993-1995 projected funding for the following: IDeA grants; The Minority High School Research Apprenticeship Program; Shared Instrumentation Grants; primate centers; extramural and intramural animal facility renovation grants; and Science Education Partnership Awards.

Dr. Vaitukaitis: The following table shows the level of funding for FY 1993 to FY 1995 in these programs:

		Program Funding Dollars in Thousands	
Program	FY 1993	FY 1994	FY 1995
IDeA GRANTS	$750,000	$785,000	$900,000
MINORITY HIGH SCHOOL RESEARCH APPRENTICESHIP	$8,755	$8,853	$9,353
SHARED INSTRUMENTATION GRANTS	$8,757	$9,000	$9,500
PRIMATE CENTERS	$40,789	$42,931	$44,648
EXTRAMURAL ANIMAL FACILITY RENOVATION GRANTS	$7,647	$4,921	$4,921
INTRAMURAL ANIMAL FACILITY RENOVATION GRANTS			
SCIENCE EDUCATION PARTNERSHIP AWARDS	$91	$750	$1000

BIOMEDICAL RESEARCH TECHNOLOGY

Mr. Smith: Identify the Biomedical Research Technology centers by type of center.

Dr. Vaitukaitis: The Biomedical Research Technology Program funded 62 centers in FY 1993. Fourteen of these were in the area of biomedical computing, 15 in the area of cellular structure and function, 32 in the area of molecular structure and function, and one in biomedical engineering. The resource centers thus provide sophisticated technologies and expertise to be accessed by investigators funded by all the NIH Institutes and Centers.

SMALL BUSINESS INNOVATION RESEARCH

Mr. Smith: Is the SBIR mechanism used extensively at your Center because of the Biomedical Research Technology program?

Dr. Vaitukaitis: While NCRR's SBIR mechanism is used extensively in the Biomedical Research Technology program, it is also used in the General Clinical Research, Comparative Medicine, Biomedical Research Support and the Biological Models and Materials Research Programs.

SHARED INSTRUMENTATION GRANTS

Mr. Smith: What is the price range for equipment purchased through the Shared Instrumentation Grant program?

Dr. Vaitukaitis: The Shared Instrumentation Grant Program provides support for expensive state-of-the-art instruments that cost at least $100,000 per instrument. There is no upper limit on the cost of the instrument, but the maximum award is $400,000.

BIOLOGICAL MODELS AND MATERIALS

Mr. Smith: Provide a 1993-1995 breakout by mechanism for the Biological Materials and Models Research program.

Dr. Vaitukaitis: The following table shows the funding by mechanism for the Biological Models and Materials Research Program for FY 1993 to FY 1995:

BMMR BUDGET Dollars in Thousands	FY 1993	FY 1994	FY 1995
RESEARCH PROJECTS	$5,014	$5,957	$6,497
RESEARCH CENTERS	$1,981	$1,674	$1,674
OTHER RESEARCH	$676	$994	$994
TOTAL RESEARCH GRANTS	$7,671	$8,625	$9,165
R&D CONTRACTS	$1,242	$1,161	$1,161
TOTAL BMMR	$8,913	$9,786	$10,326

INSTITUTIONAL DEVELOPMENT AWARDS

Mr. Smith: According to a March 4, 1994 Science article, NIH has so far declined to sign a memorandum of understanding with the National Science Foundation (NSF) developing a single philosophy for the EPSCoR-like programs run by seven Federal agencies. What concerns does NIH have with the NSF proposal? Do you think all agencies can share a set of goals for the program?

Dr. Vaitukaitis: Because the NCRR IDeA Program is different from the EPSCoR programs of the other agencies, there is no added value to a formal memorandum of understanding. NCRR has maintained extensive contacts with appropriate staff of the National Science Foundation for the past several years and that level of contact has been more than adequate to exchange information and goals about each agency's program. The Memorandum of Understanding stipulated having monthly meetings which were far in excess of the frequency of contact required for coordination.

The goals for the Federal Agencies is the same, but the approaches are quite different and reflect agency missions.

Mr. Smith: For how many years will the FY93 IDeA grantees receive NIH funds? After their grant period ends, how will they become integrated into regular NIH research programs?

Dr. Vaitukaitis: The FY 1993 grantees received one-year awards. During this year, the grantees are expected to generate sufficient pilot data to submit competitive applications to the NIH for awards through regular grant mechanisms.

Mr. Smith: Describe the FY 1994 funding cycle for IDeA grants and the volume of applications received.

Dr. Vaitukaitis: On December 10, 1993, a Request for Applications was issued by the NCRR for applications for the FY 1994 IDeA program. In response, twenty-two applications were received. These applications were reviewed for scientific and technical merit at an April meeting by an initial review group convened by the Office of Review, NCRR. The recommendations of the initial review group will undergo a second level of review in June by our National Advisory Research Resources Council. After the two levels of review are completed , we anticipate that approximately six to eight awards will be made.

Mr. Smith: Does the FY95 bill assume sufficient funding for new IDeA awards?

Dr. Vaitukaitis: The FY 1995 President's Budget request for the IDeA program is $900,000. This funding will provide support for the second year of the FY 1994 awards and possibly an additional award from the cohort of applications submitted in FY 1994.

RESEARCH TRAINING

Mr. Porter: The number of full-time training positions has increased from 39 in 1985 to 82 in 1990, 1991, and 1992. After 1993, the number has decreased each year. Do you anticipate a continued decline in the number of full-time training positions at the NCRR in the future? If so, why?

Dr. Vaitukaitis: In spite of the continued national requirements for additional well-trained individuals in laboratory animal science, we anticipate that the number of full-time NRSA training positions for this program will continue to gradually decline in the future. In FY 1994, an NIH-wide stipend increase was approved. This increase, coupled with increasing tuition and health insurance costs, has resulted in a decrease in the number of full-time training positions which can be supported.

MINORITY CLINICAL RESEARCH

Mr. Porter: Does the NCRR have any plans to develop programs to expand the pool of minority clinical researchers and the capability of minority institutions to conduct clinical research, through the General Clinical Research Centers and the Research Centers in Minority Institutions programs?

Dr. Vaitukaitis: Plans are now underway, through the RCMI and GCRC programs, to increase the pool of minority independent clinical investigators and to enhance the research capacity of appropriate minority institutions. This collaboration, along with the Minority Clinical Associate Physician (MCAP) initiative of the GCRC Program, should increase the number of minority clinical researchers. In FY 1995, the RCMI anticipates a special initiative --the RCMI Clinical Research Infrastructure Initiative -- to address this problem among its eligible grantee institutions. The initiative will allow these institutions to broaden their participation in clinical research in such areas as AIDS, diabetes, hypertension, and oral diseases that impact minority populations disproportionately. Long range, it anticipated that this initiative, along with the continuing collaboration between the RCMI and General Clinical Research Centers Program, will increase the number of underrepresented minorities trained to become independent clinical investigators as well as increase the number of underrepresented minorities who participate as research subjects for clinical research, including clinical trials.

HIGH PERFORMANCE COMPUTING

Mr. Porter: How do the high performance computing resources of the NCRR enhance research conducted by the NIH Institutes?

Dr. Vaitukaitis: Biotechnology resources developed and supported by the NCRR typically are used by investigators who receive their primary research support from the other NIH components. High performance computing is an enabling technology which cross cuts many of NCRR's Biotechnology Resource Centers. Research at the cellular and molecular levels has created a growing need for more quantitative and specific structure-function studies. Researchers also require innovative algorithms and software coupled with emerging massively parallel computer architectures to address increasingly more complex biomedical simulation and analysis tasks. Protein structure prediction, receptor-based drug design and physiological modeling are all areas of intense interest that require sophisticated high performance computing resources.

GENETIC RESEARCH

Mr. Porter: Human tissues are now needed for "Gene Transplant Therapy" research, a new era of science now rapidly growing. Are you enlarging support for human tissue and organ retrieval through National Disease Research Interchange in this particular area?

Dr. Vaitukaitis: One of the two goals of NCRR's Biological Models and Materials Research Program (BMMRP) is to support facilities which provide critical biological materials such as cell lines, microorganisms, DNA probes, human tissues and organs, and lower organisms to the biomedical research community. One such facility, the National Disease Research Interchange (NDRI), has been supported with a cooperative agreement by NCRR since FY 1989. Currently, NCRR is continuing its support of the NDRI through an administrative supplement until July 1994 while the amended NDRI application is undergoing review. Two years ago, the NCRR reduced the award to NDRI to reflect its concern that NCRR fund only core activities for the operations of NDRI. Any expansion into gene therapy for specific diseases would be appropriately supported by one of the categorical institutes.

Mr. Porter: Transgenic animals are important to the conduct of genetic research. What is the NCRR doing to develop non-mammalian and transgenic models to ensure that they are available to researchers when needed?

Dr. Vaitukaitis: The NCRR supports centers and research projects that develop and provide nonmammalian species to researchers. The NCRR also supports research projects on the development of transgenic zebrafish because genetic engineering of this and other lower organisms will produce useful models for the study of human genetic disorders.

In addition, the NCRR supports the National Resource for Induced Mutants at The Jackson Laboratory, Bar Harbor, Maine. At this center, embryos from selected transgenic and knockout animals are preserved, banked, and distributed. The center also conducts research on cryopreservation techniques. Although there are as yet no transgenic nonhuman primate models, basic research toward their development is in progress at the Wisconsin and Oregon Regional Primate Research Centers.

RESOURCE CENTERS

Mr. Porter: In contrast to other Institutes, the NCRR relies more heavily on the center mechanism. Why has the NCRR taken this approach, and are the centers cost effective?

Dr. Vaitukaitis: NCRR relies heavily, approximately two-thirds of its research funding, on the "resource center" mechanism of support. The resource center is the most appropriate mechanism of support for many technologies and resources essential to biomedical and behavioral research. The cost effective nature of resource centers is a core attribute of this mechanism of research support. Since the resources are shared among many investigators, economies of scale can be realized, thus providing a research intensive environment that reduces the time required to accomplish the research.

Characteristics of NCRR resource centers are that they provide technologies at the cutting edge; resources that are often one-of-a-kind or expensive; resources that are cost efficient and shared; environments that are multidisciplinary and collaborative, often serving to integrate diverse research efforts; and resources that are stable, yet flexible, allowing scientists to react rapidly and effectively to emerging needs and unexpected research opportunities.

BIOLOGICAL MODELS AND MATERIALS

Mr. Porter: We know that human tissue and organs and human biomaterials have become very important for many areas of disease research such as Diabetes, Cancer, and gene therapy. Have you moved to enlarge and continue support for the National Disease Research Interchange (NDRI), the national program collecting and distributing human tissue and organs for research?

Dr. Vaitukaitis: One of the NCRR missions is to support resources which provide critical biological materials such as cell lines, microorganisms, DNA probes, human tissues and organs, and lower organisms to the biomedical research community. One such facility, the National Disease Research Interchange (NDRI) has been supported with a cooperative agreement by NCRR since FY 1989. Currently, NCRR is continuing its support of the NDRI through an administrative supplement until July 1994 while the current NDRI competitive application is undergoing review. After the National Advisory Research Resources Council meeting in June, a recommendation will be made as to the appropriateness and level of funding of the NDRI. Any expansion into specific disease areas would be appropriately supported by one of the categorical institutes, such as the human tissue network to provide cancerous tissue to researchers that is currently supported by the National Cancer Institute.

Mr. Porter: You have had a directive to support "Alternatives to Animals" in research. How have you enlarged your support for human tissues and organs and other human biomaterials, DNA, and cell lines to the researchers who need them?

Dr. Vaitukaitis: In addition to providing human tissues and organs to biomedical researchers, the NCRR supports collections of valuable biomaterials such as cloned genes, DNA probes, and human chromosome libraries which are located at the American Type Culture Collection in Rockville, Maryland.

Also, NCRR supports the Center for Alternatives to Animal Testing in Baltimore, Maryland, and a large array of invertebrate and nonbiological systems for biomedical research.

EXTRAMURAL CONSTRUCTION

Mr. Stokes: When this committee provided the FY 1994 funding for Facilities Construction Program, the Committee recommendation clearly stated that 25 percent of the funds would be awarded to "Institutions of Emerging Excellence," which have been described in the law as research centers in minority institutions. Does the Center have plans to award these funds in any manner which is inconsistent with that directive?

Dr. Vaitukaitis: The NCRR stated in the Request for Applications for construction grants that up to 25 percent of the funds were targeted for institutions of emerging excellence designated under Section 739 of the Public Health Service Act as revised in PL 102-408. Institutions that had received a PHS Centers of Excellence grant award in Fiscal Year 1993 were also directly contacted to inform them of this opportunity. Thus the NCRR has made an effort to be certain that eligible "Institutions of Emerging Excellence" were aware of the program. Since review has not taken place, plans for the awards have not been made.

Mr. Stokes: What is the current status of the application process for the Biomedical Facility Construction Program? How many awards do you anticipate providing to Institutions of Emerging Excellence?

Dr. Vaitukaitis: Sixty-nine applications have been received in response to the NCRR Request for Applications for construction grant funds. The applications will be reviewed in June for scientific and technical merit based upon published review criteria by an initial review group. The National Advisory Research Resources Council will carry out the second level of review in September. Four applications have been received from institutions designated as

Institutions of Emerging Excellence. It is not possible to determine prior to review how many of these applications will be awarded.

Mr. Stokes: How does the National Center for Research Resources intend on making awards for the Biomedical Facility Construction Program?

What is the rationale behind this process?

Dr. Vaitukaitis: The primary consideration in making awards will be the scientific and technical merit of the applications. The NCRR anticipates that the special needs of Centers of Emerging Excellence will be considered by the initial review group, and included such consideration as a review factor. Staff, working with the National Advisory Research Resources Council, will work to insure that the four to ten awards to be made represent an appropriate balance between scientific merit, institutional needs and legislative intent.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Stokes: Are any Institutes co-funding Research Centers in Minority Institution Grants?

If so what projects are being conducted?

Dr. Vaitukaitis: In FY 1993, collaborative efforts among the NIAID, NCHGR, Office for Research on Minority Health, NIDR and the NCRR have enabled the RCMI Program to broaden its impact. The support provided jointly by the NCRR and NIAID enabled the RCMI grantee community to pursue a wide array of research questions such as a) the development of new antiviral drugs for treating HIV infection, b) evaluation of the mechanism and factors associated with the vertical transmission of AIDS in minority populations (African American and Hispanic American), c) a comparative analysis of the HIV viral populations associated with people in Sub-Saharan Africa (Uganda) and data for U.S. and European populations in order to assess the potential efficacy of different candidate vaccines, and d) an examination of the possible interactions of the AIDS virus and the cytomegalovirus, the major cause of blindness in AIDS patients.

The support provided by NCRR and NCHGR to the RCMI grantees enabled investigators at three institutions to pursue research related to the human genome. This support has enabled an RCMI grantee institution to expand its human leukocyte antigen (HLA) laboratory as it formulated plans to develop a repository for biologic samples from African Americans. This resource has also facilitated faculty at two RCMI grantee institutions to develop a capacity to use state-of-the-art technology in analyzing a wide array of genome information.

Through research support provided by the NCRR and the Office of Research on Minority Health, investigators at three RCMI institutions have begun or expanded their environmental health science and toxicological research. Investigators at one of the institutions are examining the array and level of trace elements such as lead, arsenic, cadmium, mercury, manganese, zinc and selenium in drinking water in Puerto Rico to assess the likelihood that a significant number of inhabitants are exposed to elevated levels of trace-metals.

Mr. Stokes: Resources for clinical research at minority institutions remain extremely limited and severely restricted thereby adversely impacting their ability to compete for grants supporting clinical trials or collaborate efforts with other Institutions to engage in such studies. These Institutions provide clinical care for minority populations which over the years have been excluded from most clinical trials. What plans are underway to address the resource need for clinical research now and in the future?

Dr. Vaitukaitis: Plans are now underway, through the RCMI and the General Clinical Research Centers programs, to address the major barriers -- inadequate opportunities for junior career development for minorities, inadequate or absent research facilities along with trained paramedical research for clinical research at minority institutions -- have precluded significant participation of minority institutions with affiliated medical schools to participate in clinical research, including clinical trials. Through the General Clinical Research Centers (GCRCs) program, an expanded number of minority Clinical Associate Physicians will be supported to increase the number of independent clinical investigators. The RCMI program will also contribute to the career development of minority clinical investigators to increase the level of expertise and number of highly qualified investigators in this area. The GCRCs also provide the opportunity for minority investigators from RCMI-funded institutions to use the expertise, specialized laboratories and clinical research facilities on a collaborative basis. Funding to the UCLA-Harbor General GCRC and Drew University Medical Center is provided through the GCRC program for collaborative studies on hypertension in Blacks and for neonatal studies of high risk Hispanic and Black infants.

Two planning meetings have already been held -- one in conjunction with the annual General Clinical Research Centers Program Directors Meeting and the other at New York University Medical Center. Draft guidelines for this special initiative -- the RCMI Clinical Research Infrastructure Initiative -- were presented and discussed. This special initiative will allow minority institutions to broaden their participation in clinical research in such areas as AIDS, diabetes, hypertension, and oral diseases that impact minority populations disproportionately. Long range, it is anticipated that this initiative, along with the continuing collaboration between the RCMI and General Clinical Research Centers Program, will increase the number of underrepresented minorities trained to become independent clinical investigators as well as increase the number of underrepresented minorities who participate as research subjects for clinical research, including clinical trials.

Mr. Stokes: How many and which Institutes, Centers, and Divisions, of the NIH are collaborating with NCRR in support of RCMI initiatives? Do you expect that this will expand in 1995?

Dr. Vaitukaitis: In FY 1994, we anticipate that the collaborative efforts between the National Center for Research Resources and the NIAID, NCHGR, ORMH, NIDR and NIDDK will continue. Staff will continue to pursue collaborative efforts with other Institutes in order to broaden these efforts in FY 1995.

RESEARCH CENTERS IN MINORITY INSTITUTIONS

Mr. Stokes: What are some of the unmet needs of the RCMI program? What are your plans to see that these needs are met? How much is included in the FY 1995 request for RCMIs, and how does this compare with 1994, 1993, and 1992?

Dr. Vaitukaitis: A major unmet need for the RCMI Program is facilitating the participation of RCMI grantee institutions in clinical research, beginning with the eight institutions with affiliated medical schools. The availability of space for biomedical research is also a very critical need and is fast becoming a rate limiting step as the institutions broaden their participation in the NIH research agenda. Finally, even though the overall competitiveness of the faculty at RCMI grantee institutions has increased significantly since the inception of the Program, many of them, like a number of good investigators, have not been able to obtain competitive/independent research support.

The increase requested for the RCMI Program in FY 1995 will be targeted to address the development of the clinical research infrastructure needs. RCMI institutions will also compete for funds to address the research space needs through the NCRR Research Facilities Improvement Program.

The funding level for the RCMI Program from FY 1992 - FY 1994, and the estimate for FY 1995 are as follows (in thousands):

Year	1992	1993	1994	1995 (Est.)
	$23,472	$23,362	$24,139	$25,346

RESEARCH TRAINING

Mr. Stokes: For America to maintain and increase its competitive edge, we must ensure an adequate pipeline of researchers trained in using the latest technologies, and capable of developing advanced technologies for tomorrow. What is your assessment of the condition of the pipeline needed to ensure continued advances in the research areas under the purview of the Center?

Dr. Vaitukaitis: In the just completed NCRR Strategic Plan, the pipeline issue was the subject of significant concern and discussion by the academic community. Included in the Plan is the objective that NCRR should "ensure the growth and strength of the Nation's scientific talent base." Some of the recommendations are that NCRR should: increase the number of clinical investigators (using the Clinical Associate Physician and Minority Clinical Associate Physician mechanisms); provide for cross-training of researchers in fields that are outside their field of specialty; maintain and expand the number of research career awards, particularly for veterinary research; expand mentorship programs for biomedical researchers, especially for those from disadvantaged backgrounds; and promote science literacy and increase public understanding of science.

MINORITY HEALTH RESEARCH

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are supported by your Institute?

Dr. Vaitukaitis: The NCRR has five major initiatives in minority health research and research training and outreach. They are the Research Centers in Minority Institutions Program (currently 19 institutions are supported: 10 at Historically Black Colleges and Universities, five at predominantly Hispanic institutions, three at both Hispanic and Black institutions and one at an Asian/Pacific Islander institution); the Minority Clinical Associate Physician Program (10 awards made in FY 1993); the Minority High School Student Research Apprenticeship Program (3,066 students and 574 teachers and 118 preservice teachers received awards in FY 1993) and the Minority Supplements to ongoing research grants (nine in FY 1993). In FY 1994 the NCRR has restarted the Research Facilities Improvement Program (RFIP), to provide support to expand, remodel, renovate or alter existing facilities or construct new research facilities. Of the $7.0 million in the RFIP, 25 percent has been targeted for Institutions of Emerging Excellence.

Mr. Stokes: How does your Institute identify its priorities for investments in minority research and research training?

Dr. Vaitukaitis: The NCRR receives advice and guidance in setting priorities for investments in minority research and research training in a number of ways. A major source of advice and guidance is the National Advisory Research Resources Council (NARRC) as well as the four chartered review committees which also have an advisory function. The NCRR Strategic Plan, which was developed with the National Advisory Research Resources Council and many members of the scientific community, addressed many issues related to minority research and research training, particularly in the sections on clinical research, research environments and human resources. Other input is received at meetings with RCMI Program Directors twice annually. This provides input to NCRR on new opportunities and other important information to guide NCRR decisions and priorities.

MINORITY EMPLOYMENT

Mr. Stokes: How many GS-15 and above positions are there in your Center? How many employees in your Center are in GS-15 and above positions? In your Center, currently, how many African Americans are at the GS-15 and above level? In what positions are they? In your Center, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the NIH requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem in your Center?

Dr. Vaitukaitis: There are 20 filled and 5 vacant positions at the GM-15 and above level. Three are filled by African Americans. The positions held by the three African Americans are: Senior Advisor to the Director; Director, Research Centers in Minority Institutions and Chief of the Scientific Equipment Services Branch. There are no cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level for African Americans. NIH has requested relief from the freeze, however it has not been granted. If the freeze were lifted the Center would be able to accelerate activities toward the Affirmative Action and FEORP goals. In the near future, after the freeze is lifted, NCRR will begin National searches to fill its vacant positions.

MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by the Center?

Dr. Vaitukaitis: In the FY 1994 Appropriation $24,139,000 is provided for the support of Research Centers in Minority Institutions. Overall, the NCRR provided approximately $25,317,000 to 42 minority institutions.

Mr. Stokes: Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack the necessary resources. Describe efforts underway to increase the level of participation by historically black colleges and universities in the Center's programs and activities?

Dr. Vaitukaitis: The RCMI Program is the principle effort within the NCRR which provides, through competitive grant support, resources to minority institutions to develop their research infrastructure. This Program was started in FY 1985 to provide competitive support to minority institutions that award doctoral degrees in the health or health-related sciences. In FY 1992, the scope of the RCMI Program was expanded to allow minority institutions with emerging doctoral programs in the health sciences to compete for one-time grant awards. Currently, the RCMI Program provides grant support to 19 institutions to assist them in developing their research infrastructure. Eleven of the 19 grantees are Historical Black Colleges and Universities.

The support provided through the RCMI Program has enabled the grantees to expand their participation in NIH funded research. For example, in FY 1984, the year before the initiation of the RCMI Program, the grantees received $27.1 million from all sources for NIH support. In FY 1993, they received $83.5 million, a more than three-fold increase since the inception of the RCMI Program. In FY 1988, RCMI grantees received about $618 thousand for AIDS and AIDS-related research. In only four years that figure increased over twenty-fold, to about $14 million.

The increase in funding, as well as the scientific advancements, are attributable, in part, to the improved research infrastructure provided by the RCMI Program and the collaboration with various NIH Institutes.

MINORITIES IN RESEARCH

Mr. Stokes: Explain the proposed funding for the programs of your Center that are designed to increase the participation of underrepresented minorities in biomedical research, and research training?

Dr. Vaitukaitis: The President's request provides for a five percent increase in support for the Research Centers in Minority Institutions ($25.346 million) and a 5.6% increase in the Minority High School Student Research Apprenticeship Program ($9.353 million). In FY 1994 the NCRR restarted the Research Facilities Improvement Program (RFIP), to provide support to expand, remodel, renovate or alter existing facilities or construct new research facilities. In FY 1995 the President requested $7 million for the Research Facilities Improvement Program to continue it at the same level as in FY 1994 with a 25 percent target for "Institutions of Emerging Excellence." In addition, the GCRC program supports the junior career development of minority physicians and dentists to become independent clinical investigators.

BIOLOGICAL MODELS AND MATERIALS

Mr. Stokes: Human tissue and biomaterial research is an important component of the biomedical research continuum. Can you bring the committee up-to-date on the initiative that is underway with the National Disease Research Interchange? What level of support is provided for this initiative in FY 1995, and 1994?

Dr. Vaitukaitis: The NCRR Biological Models and Materials Research Program (BMMRP) has a dual mission: first, the development of nonmammalian model systems, such as invertebrates, lower vertebrates, cell, tissue culture, and nonbiological systems (including mathematical and computer models) for biomedical research; and second, the support of resources which provide critical biological materials such as cell lines, microorganisms, DNA probes, human tissue, and lower organisms to the biomedical research community. Currently, the BMMRP budget is split about equally between the development of systems and resource funding. The National Disease Research Interchange (NDRI) is being supported by an administrative supplement of $447,236 through July 1994. The amended application is under review and after the National Advisory Research Resources Council (NARRC) meets in June, a recommendation will be made as to the appropriateness and level of funding for NDRI.

JOHN E. FOGARTY INTERNATIONAL CENTER

STRATEGIC PLANNING

Mr. Smith: Tell us more about the strategic planning you have done and resulting reorientation of your programs.

Dr. Schambra: As an outcome of a long range plan developed in consultation with the FIC Advisory Board and the U.S. scientific community, the FIC has identified both scientific and human resource priorities which we feel are central to our mandate. The plan builds on current program strengths and identifies important new directions for FIC. Emphasis is placed on programs to enable U.S. universities to extend the geographic base of their research and training efforts to meet disease challenges that are transnational in scope. New scientific areas have been identified that will employ the AIDS International Training and Research Program as a paradigm.

Because AIDS has demonstrated the continuing risk of emerging viruses that result from rapid ecological and social change, a natural complement to this program is to support basic studies on emerging pathogens--to help determine the epidemiologic and biologic principles that result in new or resurgent microbial diseases. This would be done by enabling NIH grant recipients to undertake cooperative research in areas of the world that are the possible future loci for new infectious diseases.

FIC also proposes to place emphasis on an equally insidious health threat--the health impacts of environmental toxins--through cooperation with regions of the world with high levels of exposure to environmental contaminants. And finally, we would place emphasis on population research in support of strategies for sustainable development--ranging from basic studies in the reproductive sciences to behavioral and demographic research.

In the area of human resource development, FIC will expand international fellowship opportunities for American scientists--which are presently concentrated on established investigators--to scientists at a more formative stage of their career. Our intent is to develop the biomedical equivalent of career development awards established under the Fulbright, Marshall and Rhodes endowments. Our premise is that the future generation of American scientists will need to be true internationalists--cooperating across national borders and understanding the geographic divergence of perspectives and cultures.

Our foreign fellowship program, the International Research Fellowship Program, was established during the latter stages of the Marshall Plan reconstruction in Europe--in part to help rebuild the science base in Europe. Most of the Fellows have come from Europe or other industrialized countries. We will refocus the program on its developmental intent by limiting eligibility to developing nations and other countries with critical research training needs and limited resources.

In addition, international policy issues are identified for FIC that require continuing analysis in support of NIH programs. These include strategies for interagency cooperation in cross-cutting fields, international competitiveness concerns, and the ethical, legal and social implications of international research, including vaccine trials.

INTERNATIONAL RESEARCH FELLOWS

Mr. Smith: You are shifting the focus of the International Research Fellows program to developing countries and reducing its funding. Is that because you believe you will be less successful in recruiting high quality candidates from these countries?

Dr. Schambra: The reduction in funding levels for the International Research Fellowship (IRF) program is an outcome of budget reductions in FIC non-AIDS programs, combined with our intent to focus the program in developing countries and to provide additional support to American scientists through the Fogarty International Research Collaboration Award and the Senior International Fellowship program.

FIC hopes in future to restore the IRF program to previous funding levels, based on availability of resources. In FY 1992, for example, FIC supported 85 new IRF awards. We are confident that the program in future could support an equivalent number of new IRFs from developing nations. In anticipation of this opportunity, FIC is exploring strategies to ensure that the program reaches the broadest geographic distribution of scientists from developing nations in Africa, Latin America and Southeast Asia, as well as emerging democracies in Europe.

BIODIVERSITY PROGRAM

Mr. Smith: How much funding are you and other NIH entities allocating to the international biodiversity program?

Dr. Schambra: The total funding level for the biodiversity program in FY 1994 is $2,450,000, which consists of $900,000 from the FIC, $550,000 from other NIH entities and $500,000 each from the National Science Foundation and the U.S. Agency for International Development.

INTERNATIONAL RESEARCH COLLABORATION AWARD

Mr. Smith: Why does your budget propose an increase in the Fogarty International Research Collaboration Award -- is this program intended to eventually replace the International Research Fellowship?

Dr. Schambra: The Fogarty International Research Collaboration Award (FIRCA) and the International Fellowship Program serve two distinct, though complementary purposes. The FIRCA is analogous to a seed grant that supports U.S. universities and research institutions to collaborate with counterparts in Russia and the new republics, Central and Eastern Europe, and Latin America. The award provides for the short-term exchange of scientists, sharing of data and research resources, and the provision of necessary supplies and materials.

The International Research Fellowship, a dedicated research training award of up to two years duration, enables postdoctoral scientists from developing nations to acquire analytic and applied skills, and to participate in research projects based at U.S. institutions.

Although these programs serve different intents, we encourage International Research Fellows and their U.S. mentors to consider the FIRCA program as a means to continue cooperation after the foreign fellow returns to his or her home country.

SENIOR INTERNATIONAL FELLOWSHIPS

Mr. Smith: Why are you proposing to increase the Senior International Fellowships that send Americans abroad rather than bring more foreign scientists to the U.S.?

Dr. Schambra: With the rapid progress of the biomedical research enterprise in Europe, Japan and elsewhere, I believe it is vital to provide new opportunities for American scientists to conduct studies at innovative laboratories abroad. As a result, we have decided to increase the number of Senior International Fellowships in FY 1995 and to begin development of a fellowship award for young American investigators.

This direction is especially timely. European laboratories are now at the vanguard of vaccine development and molecular biology in such fields as instrumentation for the analysis and synthesis of DNA and proteins, and vector systems for gene cloning and hybridoma technology. Japanese institutions contribute substantively to biotechnology, medical imaging, robotics and other basic and applied fields of biomedical science.

Less developed nations provide unique opportunities for American scientists to advance understanding of the pathogenesis and prevention of certain diseases, including AIDS, parasitic infections, and genetic disorders and cancers prevalent to specific regions. A key example is the recent discovery of the gene for Huntington's chorea, which resulted from detailed studies of a cluster of families in Venezuela afflicted with this disorder.

MINORITY PROGRAM

Mr. Smith: What is the goal of your Minority International Research Training program--to interest minority students in scientific research by sending them abroad? How much funding will be allocated to this program in 1995, and how much is the Office of Research on Minority Health contributing? How is the funding divided between the undergraduate, graduate, and faculty components?

Dr. Schambra: In cooperation with the NIH Office of Research on Minority Health, the FIC established the Minority International Research Training (MIRT) program to provide international educational, training and research opportunities to minorities underrepresented in the scientific professions. Training grants are provided to U.S. colleges and universities to stimulate students to pursue scientific careers by enhancing their undergraduate and graduate training through international experiences. Awards also are provided to faculty members to conduct independent research and to serve as mentors to students abroad.

In the first year of the program, twenty U.S. colleges and universities will participate in the program. These international partnerships involve 27 countries, incorporating academic centers in Europe, Canada, Latin America, Africa, Asia and Pacific Rim countries.

The MIRT is intended to cultivate qualities of leadership by broadening intellectual and cultural horizons. The program strives to ensure an equity of opportunity by creating and expanding programs for minority students and scientists to study abroad. An additional objective is to help ensure that the full diversity of the U.S. student population is represented abroad as young diplomats of science.

The final dollar level for the program for 1995 has not been determined, but will depend on the final appropriation for the Office of Research on Minority Health. The FIC will continue to provide the programmatic and administrative management of the program.

Approximately 45 percent of the funding will be devoted to the undergraduate component, 30 percent to the graduate component, and 25 percent to the faculty component of the program.

NEUROSCIENCE AND ENVIRONMENTAL FELLOWSHIPS

Mr. Smith: Why are you terminating your neuroscience and environmental fellowships?

Dr. Schambra: The neuroscience and environmental fellowships were designed as one-time three-year fellowships targeted to these scientific areas to enhance opportunities for Central and Eastern European scientists and health professionals to work in U.S. laboratories to exchange ideas and latest technological advances. After this initial period, the fellows would compete for continued support through the other FIC programs.

SCIENTIFIC POPULATION

Mr. Smith: Your justification mentions that there are more than 3,100 foreign scientists on the NIH campus. What percentage of the total campus scientific population does this represent?

-- Has this share changed or been fairly constant over time?

-- Is the number of foreign scientists on campus a function of supply and demand or the result of a conscious policy choice at NIH?

Dr. Schambra: Foreign scientists who work within NIH laboratories represent approximately one-third of the intramural research staff. This percentage has remained relatively constant over the past ten years. Of the 3,117 foreign scientists who conducted research in NIH intramural laboratories in FY 1993, 2,205 were supported by NIH under the Visiting Program and 912 were Guest Researchers and Special Volunteers supported by sources other than NIH.

The NIH brings foreign scientists to its campus through programs mandated by the Public Health Service Act of 1944 and the Fulbright Hays Act of 1961. These programs offer invitational fellowships to postdoctoral scientists, and temporary staff appointments to more established researchers, to enable them to conduct research within the intramural programs of NIH.

The percentage of foreign scientists on the NIH campus parallels the distribution of U.S. and foreign biomedical researchers in U.S. universities. In its 1993 report entitled Science and Engineering Indicators the National Science Foundation indicates that 48 percent of postdoctoral scientists in the biomedical sciences in the U.S. are foreign nationals.

It is not known whether this reflects an inadequate supply of U.S. students who select biomedical research as a career, since no definitive assessment exists. NIH, however, recognizes the need to attract more American students into biomedical research, especially underrepresented minorities and women, and has undertaken aggressive efforts through programs such as the National Research Service Awards for doctoral candidates, the Minority Access to Research Careers program and the FIC Minority International Research Training program.

At NIH, the participation of foreign nationals in its intramural programs reflects its historic and continuing role as a training ground for biomedical scientists throughout the world. There is a high volume of talented foreign scientists, at all career levels, who seek visiting appointments at the NIH.

The flow of international researchers to American laboratories has been a valuable part of the biomedical research effort. It has assisted NIH to sustain a highly qualified research staff and remain an international leader. Foreign scientists have contributed significantly to many NIH research advances. A recent sampling of the most productive NIH laboratories indicates that approximately two-thirds of scientific publications were co-authored by visiting researchers.

INSTITUTE OF MEDICINE REPORT

Mr. Porter: In October, the Institute of Medicine released a report on "Microbial Threats to Health in the United States." This report raises concerns about new diseases as well as older problems like malaria and tuberculosis. Are you familiar with the report, and is Fogarty addressing these issues?

Dr. Schambra: Yes, Mr. Porter I am familiar with the IOM Report on Microbial Threats to Health in the United States. In fact, Dr. Richard Krause, my Senior Scientific Advisor, served in a liaison capacity to the Committee of the IOM that drafted the report, and we reviewed the report before its publication. We have since examined its recommendations and developed initiatives within the Fogarty Center to meet the microbial threats to health in the United States. But it should be remembered that infectious diseases and epidemics know no national boundaries. AIDS is but the most dramatic example of the spread of an infectious disease worldwide. Within the last two years, cholera has occurred for the first time in the twentieth century in the Western hemisphere. There are early reports that a new more vigorous strain of cholera has emerged in Asia within the past year. So, as the Report points out, we must be vigilant and develop a more pro-active international research and surveillance network.

As I noted in my opening statement, the FIC AIDS International Research and Training Network embraces 11 U.S. institutions and scientists in research institutions in over 55 countries in Latin America, Asia, and Africa where AIDS is epidemic. This program is designed to foster epidemiology and training for foreign nationals and young U.S. scientists, but the nature of the training is such that the graduates are well-prepared to participate in any current and future efforts concerning the emergence of infectious diseases. For example, investigators in Haiti, working with scientists at Cornell, have shown that isoniazid treatment effectively decreases the incidence of tuberculosis in symptom-free HIV seropositive individuals and delays the onset of HIV-related disease.

As the AIDS epidemic moves into Asia, scientists must be on the lookout for unexpected opportunistic infections, just as tuberculosis was recognized as an opportunistic infection in AIDS patients in Africa. Here again, the FIC network has responded to the emergence of new infections. For example, in Thailand, epidemiologic studies by scientists at Chiang Mai University and Johns Hopkins have recognized the environmental reservoir of *Penicillium marmeffei* infection. This fungus is common in HIV-infected patients in Northern Thailand and is now recognized as one of the most common opportunistic infections in HIV-positive patients in that region.

It is conceivable that AIDS would have been detected while it was still confined to local regions in Africa if this international network of scientists had existed at the time. In program reviews with the Directors of our training programs in U.S. universities, we are urging them to focus attention, also, on research and training pertaining to emerging infectious diseases. This is one of the recommendations of the IOM Report. We also, of course, work closely and coordinate our efforts with the NIAID, the CDC, and WHO. Such coordination was also stressed in the recommendations of the IOM Report.

25TH ANNIVERSARY

Mr. Stokes: As the Center marked its 25th anniversary, that is an opportune time to assess the past and plan the long-term future of the Center. Can you tell us what have been the most significant accomplishments over the past 25 years?

Dr. Schambra: As a focus of NIH international activities, FIC has been instrumental in forging partnerships between U.S. and foreign scientists. As International Research Fellows (IRF), over 3,000 scientists from over 60 nations have contributed to the research pursuits of U.S. universities. Many former Fellows now are leaders within the biomedical research enterprise in their own countries and retain strong ties to the U.S. For example, the discovery of a gene responsible for the hereditary form of colon cancer was the result of cooperation between U.S and Finnish research teams, co-lead by a former IRF at the University of Helsinki.

Nearly 800 American scientists have undertaken research at leading research institutions abroad as Senior International Fellows to benefit from unique expertise or resources, ranging from new techniques in molecular biology developed at Cambridge University in the United Kingdom to potential new cancer agents derived from marine invertebrates from the coral reefs of Australia.

The Scholars-in-Residence program has enabled NIH to bring to its campus eminent researchers to explore new approaches to contemporary challenges in biology and medicine, and has fostered discoveries in molecular genetics, neurobiology, biophysics and other ascendant fields of biomedical science. Most recently, this included the isolation of the gene responsible for the abnormally high incidence of a pediatric leukemia associated with Down's syndrome.

Through international agreements administered by the FIC, avenues of cooperation were forged with Warsaw pact nations which exposed their scientists to the intellectual freedoms of the Western scientific culture and contributed to democratic change. And finally, during the late Dr. Albert Sabin's tenure at the FIC, global immunization strategies were mobilized that resulted in the virtual eradication of polio from the Americas.

As FIC enters its second quarter century, the Center will build on the scientific enterprise--now global in scope--to meet new and emerging scientific and human resource challenges.

Mr. Stokes: What are some of the most significant plans and goals for the future?

Dr. Schambra: As an outcome of a long-range plan developed in consultation with the FIC Advisory Board and the U.S. scientific community, the FIC has identified both scientific and human resource priorities which we feel are central to our mandate. The plan builds on current program strengths and identifies important new directions for FIC. Emphasis will be placed on programs to enable U.S. universities to extend the geographic base of their research and research training efforts to meet disease challenges that are transnational in scope. New scientific areas have been identified that will employ FIC's AIDS International Training and Research Program as a model.

Because AIDS has demonstrated the continuing risk of emerging viruses that result from rapid ecological and social change, a natural complement to this program is to support studies on emerging pathogens--to help determine the epidemiologic and biologic principles that result in new or resurgent microbial diseases. This would be done by enabling NIH grant recipients to undertake cooperative research in areas of the world that are the possible future loci for new infectious diseases.

FIC also proposes to place emphasis on an equally insidious health threat--the health impacts of environmental toxins through cooperation with regions of the world with high levels of exposure. And finally, we would place emphasis on population research in support of strategies for sustainable development--ranging from basic studies in the reproductive sciences to behavioral and demographic research.

In the area of human resource development, the FIC will expand international fellowship opportunities for American scientists--which are presently concentrated on established investigators--to scientists at a more formative stage of their career. Our intent is to develop the biomedical equivalent of career development awards established under the Fulbright, Marshall and Rhodes endowments. Our premise is that the future generation of American scientists will need to be true internationalists--cooperating across national borders and understanding the geographic divergence of perspectives and cultures.

Our fellowship program to support studies conducted by foreign scientists in the U.S., the International Research Fellowship Program, was established during the latter stages of the Marshall Plan reconstruction in Europe--in part to help rebuild the science base in Europe. Most of the Fellows have come from Europe or other industrialized countries. We will refocus the program on its developmental intent by limiting eligibility to developing nations and other countries with critical research training needs and limited resources.

In addition, international policy issues are identified for FIC that require continuing analysis in support of NIH programs. These include strategies for interagency cooperation in cross-cutting fields, international competitiveness concerns, and the ethical, legal and social implications of international research, including vaccine trials.

HEALTH AND POPULATION INITIATIVE

Mr. Stokes: What are the major goals and objectives of the Center's health and population initiative?

Dr. Schambra: The intent of this initiative is to create research and research training partnerships between U.S. institutions and scientists in regions of the world experiencing population growth which has, or will have, adverse impacts on public health, the environment and economic development. The initiative will enable American scientists to conduct studies that could not be realized in the U.S. alone and assist to train a cadre of research and health professionals in developing nations to assist their countries to develop effective population policies. The program is being developed in consultation with the National Institute of Child Health and Human Development and will provide support to its research centers and other institutions with major programs in population research.

Of the projected global population increase of some 3.2 billion over the next few decades, it is estimated that at least 3 billion, or 95 percent, will be in the less developed countries. This trend has significant ramifications for global health. In developing nations, high birth rates may outstrip sustainable economic development. Consequences may include increasing pollution and worsening sanitation, the spread and emergence of infectious diseases, overexploitation of land, destruction of natural ecosystems, unemployment, and inadequate access to health care and education. Through international research and research training efforts, the FIC is positioned to advance technological and social adaptations needed to face the challenge of unsustainable population growth.

COLLABORATIVE LINKAGES WITH NIH INSTITUTES

Mr. Stokes: To what extent is there collaborative linkages with Institutes of the NIH, explain.

Dr. Schambra: In a reciprocal manner that NIH Institutes, Centers and Divisions (ICDs) consult the FIC on issues of international policy and program administration, the FIC works extensively with the ICDs in programmatic development to support their missions through international programs. A majority of FIC programs directly support NIH grant recipients and provide an international dimension to ongoing studies.

For example, the Fogarty International Research Collaboration Award (FIRCA) supports cooperative activities between American scientists supported by the NIH and their counterparts in Russia and the new republics, Central and Eastern Europe, Latin America and Africa. The AIDS International Training and Research Program enables NIH grant recipients at the vanguard of AIDS research to conduct field studies that require international cooperation and to develop a cadre of foreign counterparts to participate in international trials to test HIV vaccines and other interventions.

In addition, the Scholars-in-Residence program enables NIH intramural scientists to interact with prominent visiting scholars to gain new insights and perspectives. A leading attribute of the program has been to promote interdisciplinary approaches to biomedical challenges on the NIH campus and beyond, and to signal promising new areas of biomedical research, such as gene therapy and recombinant DNA approaches to new vaccines.

EFFORTS AFFECTING MINORITIES

Mr. Stokes: Please describe the measures your Center takes to ensure that research and research training, and outreach needed to address diseases and disorders disproportionately affecting minorities are conducted and supported?

Dr. Schambra: Through its diverse research and research training programs, the FIC fosters international cooperation on diseases and disorders which affect minority Americans in disproportionate numbers, especially HIV/AIDS and tuberculosis. FIC-supported scientists at the University of Miami have played a key role in identifying strategies for community-based treatment of pediatric HIV/AIDS in Hispanic and African-American communities. In addition, the FIC supported a randomized trial which demonstrated the efficacy of the antibiotic isoniazid in decreasing the incidence of tuberculosis and delaying the onset of HIV-related disease in symptom-free HIV seropositive individuals. This finding has significant implications for public health programs in the inner-city, where the prevalence of tuberculosis has resurged.

The FIC also supported research on iron deficiency anemia and infant behavior as well as studies on the relation of social, environmental, and nutritional conditions causing infant mortality, both of which are of importance to minorities.

MINORITY INITIATIVES

Mr. Stokes: What significant initiatives in minority health research and research training, and outreach are funded by your Center?

Dr. Schambra: In cooperation with the NIH Office of Research on Minority Health, the FIC has established a Minority International Research Training (MIRT) program to provide international research training opportunities to minorities underrepresented in the American biomedical community. Training grants are provided to U.S. colleges and universities to stimulate students to pursue scientific careers by enhancing their undergraduate and graduate training through international research training experiences. Awards also are provided to faculty members to conduct independent research and to serve as mentors to minority students abroad.

In the first year of the program, over twenty U.S. colleges and universities will participate in the program, many through consortia of large and smaller institutions. Eight HBCUs are also included in the new program. These international partnerships involve 27 countries, incorporating academic centers in Europe, Canada, Latin America, Africa, Asia and Pacific Rim countries.

The MIRT is intended to cultivate qualities of leadership by broadening intellectual and cultural horizons. The program strives to ensure an equity of opportunity by creating and expanding programs for minority students and scientists to study abroad. An additional objective is to help ensure that the full diversity of the U.S. student population is represented abroad as young diplomats of science.

Mr. Stokes: How does the Center identify its priorities for investments in minority research and research training?

Dr. Schambra: FIC convenes the principal investigators of the MIRT program annually to discuss programmatic strategies. This serves as an excellent forum to identify opportunities and needs related to the recruitment and retention of minorities in the biomedical sciences and other research and training concerns related to minority Americans. Future topics of discussion will include minority health issues, including unique opportunities to advance our understanding of diseases and disorders affecting minority populations through international programs.

MINORITY FUNDING

Mr. Stokes: When the Office of Research on Minority Health provides funds to the Center, do these funds typically augment existing minority programs or efforts, or do they replace funds your Center previously invested in its minority research and research training initiatives, elaborate.

Dr. Schambra: The funds received from the Office of Research on Minority Health in FY 1993 were used to augment minority efforts through FIC's new Minority International Research and Training Program; to supplement FIC's AIDS International Training and Research Awards to recruit American minority scientists into the program to increase clinical and epidemiological skills related to HIV/AIDS; and to support five Fogarty International Research Collaboration Awards, two Senior International Fellowships and one International Research Fellowship to provide support for activities related to minority health or for minority investigators.

Mr. Stokes: When your Center is developing new minority initiatives, does it seek advice from the Office of Research on Minority Health? To what extent is there a collaborate relationship between the two organizations, elaborate.

Dr. Schambra: Yes, the FIC does seek advice and guidance from the Office of Research on Minority Health (ORMH) in developing new minority initiatives. In fact, we worked very closely with the ORMH in the development of the Minority International Research Training (MIRT) program. We jointly sponsored a workshop in October 1992 to explore "international opportunities for minority students and scientists," in biomedical and behavioral research that led to the MIRT program. Following the awards, we also jointly held a network meeting of the awardees in October, 1993. While we provide the programmatic and administrative management of the program, we continue to consult with the ORMH on the future directions of the program.

HBCUS

Mr. Stokes: What are some of the major initiatives underway at your Center to increase participation of historically black colleges and universities in biomedical research?

Dr. Schambra: Although the MIRT program is open to all U.S. colleges and universities, special efforts are undertaken to encourage the participation of Historically Black College and Universities (HBCUs) through site visits and other measures. As a result of these efforts, 8 of the 20 institutions supported under this initiative in its first year of funding are HBCUs.

The MIRT also incorporates consortia awards that include partnerships between majority and minority institutions. A long-term objective of these consortia is to increase cooperation between minority and majority institutions and to strengthen an important educational "pipeline" by exposing students at two- and four-year minority institutions to major research universities. It is estimated that, due to lack of exposure to doctoral programs in the U.S., many promising undergraduates at four-year minority institutions may not make the transition to research universities to pursue higher degrees.

FIC STAFFING

Mr. Stokes: How many GS-15 and above positions are there at the Center? How many employees in your Center are in GS-15 and above positions? Currently, how many African Americans are at the GS-15 and above level? In what positions are they? At the Center, how many African Americans are among the cases pending for exception to the freeze on appointments and promotions to the GS-15 and above level? Has the Center requested relief from the freeze, if so, what was the response? If the freeze were lifted, how would it help the EEO problem in the Center?

Dr. Schambra: The Fogarty Center has 11 positions at the GS-15 and above level of which none are African Americans. However, the Center has one Hispanic female Branch Chief and one Asian male Assistant Director/Branch Chief at that level. The Center does not have any cases pending for appointment and promotion to the GS-15 and above level. The Center has submitted two requests for exception to the freeze, one for a GS-5 Office Automation Assistant and the other for a GS-5 International Program Assistant both of whom are minorities. We have just received approval for one of the exceptions. If the freeze were lifted, the Center would continue to make every effort to recruit and select qualified minority staff.

SUPPORT FOR MINORITY INSTITUTIONS

Mr. Stokes: What is the present level of support provided to minority institutions by the Center?

Dr. Schambra: In FY 1994, the FIC expects to spend approximately $700 thousand for minority activities, in addition to the funds provided by the Office of Research on Minority Health for the Minority International Research Training (MIRT) program.

Mr. Stokes: Minority institutions seem to face a "catch 22" situation. They are often told that they cannot get funding because they do not have the appropriate infrastructure. However, they cannot develop the appropriate infrastructure because they lack necessary resources. Describe efforts underway to increase the level of participation by Historically Black Colleges and Universities in the Centers programs and Activities.

Dr. Schambra: As described above, the FIC has ensured the meaningful participation of HBCUs in its MIRT program through directed staff efforts, such as site visits, and through program development that encourages cooperation with larger U.S. universities that are traditionally competitive for NIH awards.

UNDERREPRESENTED MINORITIES

Mr. Stokes: Explain the proposed funding for the programs of your Center that are designed to increase the participation of underrepresented minorities in biomedical research, and research training.

Dr. Schambra: The MIRT represents the major FIC initiative to support this critical effort. We are currently in a second competitive cycle and expect to make additional new MIRT awards by the end of FY 1994. In addition to this expansive program, FIC encourages minority participation in its programs through special efforts to inform minority scientists of FIC research and research training opportunities. These efforts include participation at conferences involving recipients of the Minority Access to Research Careers (MARC) and Minority Biomedical Research Support (MBRS) programs, site visits to HBCUs, special mailings to minority scientists and HBCUs, and assistance to the NIH Grants Associates Board to develop initiatives to recruit minorities as NIH professionals.

MEXICO

Mr. Bonilla: You state in your written testimony that FIC now supports an award program open to research collaboration with several continents. Could you describe what types of projects FIC has with the country of Mexico and what the projects are designed to accomplish?

Dr. Schambra: In FY 1990, the Fogarty International Center (FIC) developed a Latin American and Caribbean Initiative (LACI) to increase research cooperation between U.S. biomedical and behavioral scientists and scientists with Mexico and other countries in the region. The LACI has supported advanced research training to equip Mexican scientists for future collaboration in molecular biology and the pharmacology of neuropeptides, neuroepidemiology, and oral health. Mexican and U.S. scientists also were supported to conduct an exploratory study among Pima Indians in Arizona and Mexico to clarify the role of genetics and environment in obesity and non-insulin dependent diabetes. Another collaborative study contributed significant findings on the role of two of the most important intestinal protozoal pathogens, Giardia lamblia and Entamoeba histolyica, as opportunistic infections in immunocompromised individuals.

In FY 1992, I represented the National Institutes of Health (NIH), on a Public Health Service delegation visit to the Mexican National Institute of Social Security (IMSS) to explore opportunities for joint health sciences cooperation. The visit, requested by the U.S. State Department and Dr. Louis Sullivan, then Secretary of Health and Human Services, resulted in FIC sponsorship of NIH-IMSS exchange visits to identify areas of cooperation. The FIC and IMSS are now discussing plans for a workshop to develop research projects of mutual priority.

Since FY 1992, the FIC and the Mexican National Council for Science and Technology (CONACYT) have been working to promote increased U.S.-Mexico health sciences cooperation in the North American Free Trade Agreement (NAFTA) era. An NIH-CONACYT agreement to establish a U.S.-Mexico Biomedical Research Program is in final stages of negotiation. In February, 1994, a CONACYT-NIH health sciences research development workshop was held in Cuernavaca, Mexico, where 19 U.S. scientists and 18 Mexican scientists met to discuss on-going research and the potential for future collaboration in neurobiology, cellular immunology, and infectious and parasitic diseases, including HIV/AIDS.

Discussions have begun on a second CONACYT-NIH workshop to focus on environmentally and socially-induced diseases (environmental health, sexually-transmitted diseases, and addictions). In a recent meeting with the President of the Medical Research Council of Canada (MRCC), the MRCC expressed interest in participation, providing an important step in North American cooperation in the NAFTA era. The FIC represented NIH at a CONACYT meeting in Acapulco, Mexico, to explore U.S.-Mexico-Canada cooperation in science and technology. The health sciences working group recommended opportunities for trilateral cooperation, and the FIC is exploring the development of a trilateral working group to plan activities of joint priority.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FISCAL YEAR 1995

Volume III

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
Overview
National Cancer Institute
National Heart, Lung and Blood Institute
National Institute of Dental Research

Justification of
Estimates for
Appropriations Committees

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

	FY 1995 Estimate		Page
	FTEs	Amount	Number
Overview	---	---	1
National Cancer Institute	2,331	$1,967,709,000	49
National Heart, Lung and Blood Institute	859	1,266,961,000	113
National Institute of Dental Research	351	163,776,000	159

Department of Health and Human Services
Public Health Service
THE NATIONAL INSTITUTES OF HEALTH

FY 1995 Congressional Justification
Overview

I. THE NIH MISSION

As this Nation's principal federally-supported biomedical research investment, the National Institutes of Health (NIH) is an integral part of the Administration's commitment to improving the health and quality of life of its citizens. Through the conduct, support and promotion of biomedical research, NIH pursues science to expand fundamental knowledge about the nature and behavior of living systems, to apply that knowledge to extend the health of human lives, and to reduce the burdens resulting from disease and disability. NIH's support of more than 50,000 scientists working at 1,700 institutions across the U.S. yields rich and varied returns in the form of advances leading to new therapeutic and diagnostic methods, more effective approaches to health promotion and disease prevention, and savings in health-care expenditures.

II. INTRODUCTION

NIH continues to play a pivotal role in the Nation's support of biomedical research. Within the panoply of research activities that comprise this investment, basic science is fundamental to discoveries and breakthroughs that enable us to extend the human life span through the prevention of such deadly diseases as AIDS and tuberculosis, and improve the quality of life by delaying the onset of diseases such as Alzheimer's and osteoporosis. Some major discoveries create opportunities for new strategies in the diagnosis, treatment and prevention of disease. Some have resulted in advances in the application of treatment and prevention strategies. Other basic scientific advances enhance understanding of the biological and psychological complexities of human health and behavior, and sow the seeds for future progress against disease and disability.

NIH's priorities in FY 1995 include:

- Reaffirming support for basic science as the core of this Nation's biomedical research agenda;
- Strengthening the integration of prevention and prevention-related research through continued support for biomedical, social, behavioral and health promotion research programs to accomplish long-range national priorities for health care reform;
- Promoting the Secretary's key themes within the Department of Health and Human Services: to promote strategic planning and early intervention as techniques in preventing future problems; to enhance NIH's interactions with the various participants in this Nation's biomedical research enterprise, including academia and the private sector.

III. FY 1994 BUDGET POLICY

The FY 1994 Appropriations Act for the Departments of Labor, Health and Human Services, and Education (P.L. 103-112) provides the NIH net appropriations of $10,955,773,000, a 6.1 percent increase above the FY 1993 budget authority of $10,325,604,000. Included in the FY 1994 appropriation is $9,654,728,000 for non-AIDS research programs, a 4.3 percent increase above the FY 1993 enacted budget, and $1,301,045,000 for AIDS-related research programs, a 21.4 percent increase above the FY 1993 enacted budget.

In FY 1994 NIH continues to support priority areas of research including minority and women's health research, tuberculosis (TB) research, childhood vaccine development, and human immunodeficiency virus (HIV)/AIDS research. Increases are provided as follows:

- High Performance Computing (HPC) (+$12.0 million) for projects to support development of advanced technologies that are essential to biomedical research.

- Patient care information systems (+$8.0 million) in the National Library of Medicine (NLM) to link physicians, hospitals and research institutions to improve the quality and effectiveness of treatment and clinical care.

- HIV/AIDS research (+$230.0 million) to find new ways to treat and prevent, and seek to cure HIV/AIDS infection.

- Breast cancer research (+$72.0 million) to expand support for this complex and devastating disease that is the most frequently diagnosed major tumor in women. These cancers are responsible for 32 percent of all female cancers and the leading cause of death in women ages 40-44. NIH supports a multi-faceted and coordinated breast cancer research program in basic research, prevention, treatment, rehabilitation, and community outreach.

- Vaccine development (+$63.0 million) to contribute to disease prevention, primarily among children.

- Women's health initiatives (+$18.0 million) to support studies planned for the third year of the Women's Health Initiative and to expand support for women's health research.

- Minority Health Initiative (+$15.0 million) to increase support for a variety of research initiatives including research in kidney disease, breast cancer, and diabetes.

- TB Research (+$12.0 million) for research in the diagnosis and treatment of TB, recognized as an emerging health crisis in the U.S.

In order to maintain a level of support needed to ensure a reliable continuum of creative and highly qualified scientists entering into research careers, NIH, in FY 1994, instituted a stipend increase for trainees supported through the National Research Service Awards (NRSA) program. Since FY 1991, stipend levels for the range of pre- and postdoctoral fellows supported through the NRSA program have not increased. Thus, NIH instituted a minimal stipend increase of $1,200 at the undergraduate predoctoral level and an increase of $1,000 at the 0-1 year postdoctoral level. The stipend increase was funded within the funds available for NRSAs through a reduction in the number of trainees supported by nearly 600 FTTPs. A total of 14,388 FTTPS will be supported in FY 1994, an increase of 97 above FY 1993.

IV. FY 1995 BUDGET POLICY

The following table represents total NIH funding levels for the last five years, including AIDS.

History of Budget Authority
(Dollars in thousands)

Fiscal Year	Non-AIDS	Percent Change	AIDS	Percent Change	Total	Percent Change
1991	$8,328,384		$1,012,469		$9,340,853	
1992	9,012,934	8.2%	1,047,456	3.5%	10,060,390	7.7%
1993	9,254,147	2.7%	1,071,457	2.3%	10,325,604	2.6%
1994 Approp.	9,654,728	4.3%	1,301,045	21.4%	10,955,773	6.1%
1995 Pres.Bud.	10,093,948	4.5%	1,379,052	6.0%	11,473,000	4.7%
5-yr. Ave. % Increase		4.9%		8.3%		5.3%

Increases in the NIH commitment to AIDS research through the same five-year period have averaged 8.3 percent compared to average increases of 4.9 percent for non-AIDS research.

In FY 1995, NIH will continue to embrace the Administration's commitment to basic scientific research. FY 1995 funding will support the momentum already gained by recent unprecedented scientific breakthroughs and profound changes in our understanding of biology. These breakthroughs will ultimately improve the well-being and quality of life of our Nation's citizens, by preventing disease, contributing substantially to U.S. competitiveness in the world's high technology markets, and reducing health care costs.

Central to the mission of the NIH and its Institutes, Centers, and Divisions (ICDs) is the mandate to support the highest quality biomedical research. Through the development of research strategies, a two-tiered system of peer-review, including Institute advisory and review boards comprised of this Nation's top scientists and health professionals, NIH and its Institutes preserve the research alliance essential to the long-term scientific and technological vitality of the U.S.

The NIH intramural program is currently undergoing a fundamental review by an independent advisory team composed of distinguished scientists from major research institutions throughout the U.S. Results of this review will help to guide the NIH intramural program in future years to best fit the needs of the U.S. biomedical research enterprise. The current program provides opportunities for investigators to develop leading edge research programs in financially secure and intellectually rich environments. It also supports an environment for trans-Institute interdisciplinary research teams to conduct the highest quality research.

The administration of the NIH Acquired Immunodeficiency Syndrome (AIDS) program will be revised in FY 1995 to reflect the mandates of the NIH Revitalization Act of 1993 (P.L. 103-43) which requires that a Director of the NIH Office of AIDS Research (OAR) be appointed to "act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the NIH." AIDS activities will continue to be carried out within the NIH Institutes, Centers, and Divisions (ICDs). However, the appropriation to support these activities will go directly to the Director, OAR, who is authorized to use transfer authority to allocate funds to the ICDs for support of their AIDS research activities.

COST MANAGEMENT

The initial NIH Financial Management Plan (FMP) was developed in FY 1991 in response to a particular set of conditions and demands which existed at that time. In FY 1994, with several years of experience and the encouragement of Congress, NIH began the process of modifying the FMP to develop more broadly applicable principles of financial management. However, as the updated FMP has not yet been completed, the FY 1995 President's Budget has been formulated in accordance with the cost management principles and funding strategies outlined in the original FMP.

Through the FMP, NIH intends to balance the necessity of operating within limited federal resources with NIH's goal of expanding fundamental knowledge about living systems to improve human health. The FMP seeks to achieve these goals by providing the funding stability necessary to maintain momentum in biomedical research advances and by supporting the most highly meritorious new initiatives to accelerate progress in biomedical research. These goals are fundamental to the credibility of the FMP with the scientific community and Congress. Within the research projects grant (RPG) portfolio, stability translates into ensuring that grants will be supported throughout the average four year life of the grant award at committed levels and that new and expanded research projects will be supported at levels appropriate to funding the most promising research within available funds.

Noncompeting grants will receive committed levels of support based on an average annual direct cost increase of four percent. As stated in the FMP, the aggregate costs of all noncompeting grants in any one fiscal year (which result from competing grants awarded in different fiscal years) will actually increase by more than four percent over the previous year. This is the result of the expiration of older, less costly grants and the influx of new, more expensive grants as well as changes in the composition of the diverse RPG portfolio as grants cycle between competing and noncompeting. These factors cause the FY 1995 aggregate average cost of noncompeting grants to increase by 6.1 percent. The average total cost of competing grants will not increase by more than the Biomedical Research and Development Price Index (BRDPI), 4.1 percent in FY 1995, over the average cost of competing grants in the previous year.

The FMP also ensures that opportunities for addressing public health emergencies or unique programmatic initiatives will be identified separately from the funding base addressed in the plan. On an ongoing basis, several groups of promising but expensive clinical trials go through competing cycles together above the funding base identified in the plan. These trials follow the same research protocol at multiple institutions because there are insufficient numbers of subjects available at a single institution to conduct a major clinical trial. These trials are the AIDS Adult and Pediatric Clinical Trials, which competed in FY 1993, supported by National Institute of Allergy and Infectious Diseases and two trials supported by the National Institute of Diabetes, Digestive and Kidney Diseases which competed in FY 1994, Diabetes Control and Complications and Modification of Diet in Renal Disease.

Consistent with the flexibility to address public health emergencies noted in the FMP, in FY 1994 NIH funded an unusually large number of competing AIDS RPGs which are on average more expensive than non-AIDS grants. In FY 1995, as these expensive grants convert to noncompeting status, competing AIDS RPGs will constitute a smaller percent of the competing grant portfolio and average costs for all competing RPGs will increase by 2.7 percent in the aggregate, less than the BRDPI of 4.1 percent. In total, NIH will fund 23,890 research project grants for $6,210,266,000, reflecting an aggregate average cost increase of 4.8 percent, including AIDS.

MAJOR AREAS OF RESEARCH

The FY 1995 President's Budget for the NIH totals $11,473,000,000, a $517,227,000, or 4.7 percent, increase above the FY 1994 appropriation. NIH will continue to respond to the national crisis in the HIV/AIDS epidemic by increasing total AIDS research support by 6.0 percent above the FY 1994 appropriation. In addition, the FY 1995 President's Budget reflects a commitment to expand specific high priority areas of research: 1) breast cancer research, and other women's health research; 2) minority health research; 3) tuberculosis research; and, 4) technological advances in High Performance Computing, as follows:

- Breast cancer research (+$86.3 million; Total: $386.8 million) The NIH supports a multi-faceted and coordinated breast cancer research program in basic research, prevention, treatment, rehabilitation, and community outreach. Funding has increased by $54.0 million above FY 1994 to support these efforts to accelerate the momentum of research discoveries and subsequent breakthroughs in breast cancer. Within this amount, $10.0 million will be directed to support the Secretary's Breast Cancer Action Plan in the National Cancer Institute's Cancer Control Program.

- TB research (+$5.8 million; Total: $52.5 million) NIH will continue to expand research efforts to help speed the advancement of knowledge needed to treat, cure, and, most importantly, prevent the continued spread of TB. With additional funds, the NIH will accelerate its TB research program on all fronts, including basic research into the causative organism, improvements in diagnostic capabilities, and development of new treatment therapies and preventive vaccines.

- Office of Research on Women's Health (ORWH) (+$5.6 million; Total: $15.9 million) ORWH will continue its support for research relating to women in reproductive health and sexually-transmitted diseases (STDs); endometriosis, leiomyomata uteri, and menopause; urological diseases and conditions affecting women across their life spans; occupational health issues, including the physiological differences between men and women that make them more or less susceptible to particular hazards in the workplace; and studies on the etiology and pathogenetic mechanisms involved in autoimmune diseases to which women are especially vulnerable.

- High Performance Computing (HPC)(+$24.0 million; Total: $81.8 million) Federal involvement in the development and early deployment of biomedical research applications for computing and high speed digital communications is critical to the development of clinical applications from basic research discoveries. Further, HPC technologies development is central to the deployment of quality health care throughout the U.S. NLM will strengthen support for the development of networks for linking hospitals, clinics, doctor's offices, medical schools, medical libraries, and universities to enable health care providers and researchers to share medical data and imagery. "Collaborative technology" will be expanded to allow several health care providers in remote locations to provide treatment to patients. In addition, database technology for storing, accessing, and transmitting patients' medical records will be expanded, while protecting the accuracy and privacy of those records.

- The Minority Health Initiative (+$10.0 million; Total: $66.5 million) This increase will support the expansion of research on injury-related morbidity, lead poisoning, asthma, learning disorders and vision and speech impairment among minority children, a community-based health behavior intervention program to lower the unacceptably high rates of morbidity and mortality among minority youth, and research in kidney disease, diabetes in blacks and hispanic women, hypertension in blacks, glaucoma, AIDS and breast cancer. NIH will expand its commitment to improve the health status of minorities by increasing programs that address the underrepresentation of minorities as researchers, and support minority research and training. Further, NIH will support programs that increase minority participation in research and pilot projects that identify effective methods to disseminate information to improve minority health.

- HIV/AIDS-related research (+$78.0 million; Total: $1,379.1 million) HIV/AIDS-related research will receive a 6.0 percent increase above the FY 1994 Appropriation. $10.0 million of this increase will be focussed exclusively on research to develop safe, effective microbicides designed for use by women to prevent sexually-transmitted infections, including HIV infection and other sexually-transmitted diseases. Growth in our understanding of the etiology and pathogenesis of HIV, and the difficulties in diagnosis and treatment associated with this disease have been significant. Accelerated investment in HIV/AIDS research will have a profound effect on containment of increasingly burdensome costs of care and treatment of this debilitating and currently fatal disease. HIV/AIDS research may benefit every aspect of this Nation's biomedical research enterprise by contributing to the essential knowledge base that leads to the prevention and cure of disease.

V. ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Because of the importance placed on HIV/AIDS research by this Administration, and in compliance with the NIH Revitalization Act of 1993 (P.L. 103-43), this budget reflects a significant change in the manner in which HIV/AIDS research funds will be allocated among the ICDs. Revisions in this legislation will be adopted in FY 1995 to provide centralized planning, coordination, and evaluation of NIH's efforts in HIV/AIDS related research. This centralized coordination of research will contribute to increased effectiveness in our Nation's research efforts to arrest this epidemic. An advisory committee as well as coordinating committees for each of the major HIV/AIDS research disciplines have been established to provide the Director, OAR, with recommendations related to HIV/AIDS activities. This advisory committee will perform in the same capacity as other NIH chartered advisory committees.

To further enhance the administration of this program, the *NIH Plan for HIV-Related Research* will serve to coordinate and prioritize NIH's HIV/AIDS-related efforts. The Director, OAR, will oversee the implementation, coordination, and evaluation of the Plan and allocate funds to the ICDs in accordance with the Plan. The objectives of the Plan will be reviewed annually and revised, if necessary, by the coordinating committees. These recommendations will be provided to the Director, OAR for consideration in the annual revision of the Plan. These efforts will serve to maximize the NIH's research investment in HIV/AIDS by eliminating potential project duplication and overlap, and to reflect the most recent scientific breakthroughs. An alternative budget, or bypass budget, for carrying out the Plan without regard to fiscal constraints, will be submitted each fiscal year to the President for review and transmittal to the Congress.

To implement the requirements of the Act, a single appropriation to the Director, OAR is being proposed for HIV/AIDS research. Through the use of transfer authority the Director, OAR, within 15 days of receipt of funds, will allocate to the ICDs all amounts available for carrying out existing AIDS activities. Within 30 days, the Director, OAR, will allocate to the ICDs the remaining amounts available for new and competing AIDS research activities.

The use of transfer authority is the most expeditious means through which the Director, OAR, can allocate the HIV/AIDS appropriation to the ICDs because, unlike other mechanisms for distribution of funds, i.e., intraagency agreements or reimbursable agreements, real transfers ensure that the HIV/AIDS budget is provided to the ICDs in a timely manner to prevent disruptions in research efforts.

The funds obligated by the Office of AIDS Research will include program management funds and amounts associated with the research development fund, i.e., the HIV/AIDS discretionary fund, included in the authorization legislation for NIH.

DHHS – NATIONAL INSTITUTES OF HEALTH

FY 1995 INCREASES BY ICD

(Dollars in Thousands)

ICD	AIDS AND NON–AIDS INCREASES											
	AIDS		NON–AIDS						FY 1995	FY 1995		FY 1995
	(+10 M) Topical Microbicides	+78 M AIDS	+ 5 M TB	+ 5 M Office of Res. Women's Hlth	+ 24 M HPCC	+ 10 M Breast Act Pln.	+ 74 M Breast Cancer	+ 10 M Min Hlth Init.	Subtotal Major Areas of Increase	+307.5 M Other Non–AIDS	Total Non–AIDS	Total Increases
FY 1994 BASE	($15,000)	$1,301,045	$46,658	$10,325	$57,800	$0	$316,595	$56,478	$1,788,901	$9,166,872	$9,654,728	$10,955,773
NCI					2,600	10,000	50,703		63,303	35,596	98,899	98,899
NHLBI							2,171		2,171	41,887	44,058	44,058
NIDR							0		0	5,687	5,687	5,687
NIDDK							6,005		6,005	19,879	25,884	25,884
NINDS							0		0	21,898	21,898	21,898
NIAID			5,806				0		5,806	16,266	22,072	22,072
NIGMS							5,409		5,409	25,214	30,623	30,623
NICHD							1,342		1,342	16,625	17,967	17,967
NEI							77		77	10,066	10,143	10,143
NIEHS							3,335		3,335	5,979	9,314	9,314
NIA							1,399		1,399	13,663	15,062	15,062
NIAMS							0		0	7,928	7,928	7,928
NIDCD							0		0	5,813	5,813	5,813
NIMH							1,269		1,269	17,692	18,961	18,961
NIDA							0		0	10,138	10,138	10,138
NIAAA							663		663	5,675	6,338	6,338
NINR							850		850	902	1,752	1,752
NCRR					6,800		562		7,362	8,500	15,862	15,862
NCHGR							2,559		2,559	20,750	23,309	23,309
FIC							1		1	919	920	920
NLM					14,600		0		14,600	3,831	18,431	18,431
OD				5,601			0	10,000	15,601	10,060	25,661	25,661
B&F							0		0	2,500	2,500	2,500
OAR	(10,000)	78,007					0		78,007		0	78,007
TOTAL INCREASE	(10,000)	78,007	5,806	5,601	24,000	10,000	76,345	10,000	209,759	307,468	439,220	517,227
FY 1995 TOTAL	(25,000)	1,379,052	52,464	15,926	81,800	10,000	392,940	66,478	1,998,660	9,474,340	10,093,948	11,473,000

DHHS – NATIONAL INSTITUTES OF HEALTH
FY 1995 Congressional Justification

Summary of Appropriations

TOTAL, NIH

	FY 1993 Budget Authority	FY 1994 Estimate	FY 1995 President's Budget
NCI	$1,805,391,000	$1,868,810,000	$1,967,709,000
NHLBI	1,166,682,000	1,222,903,000	1,266,961,000
NIDR	152,767,000	158,089,000	163,776,000
NIDDK	674,226,000	705,616,000	731,500,000
NINDS	581,072,000	608,545,000	630,443,000
NIAID	524,529,000	520,792,000	542,864,000
NIGMS	815,385,000	851,566,000	882,189,000
NICHD	488,960,000	498,769,000	516,736,000
NEI	269,634,000	281,879,000	292,022,000
NIEHS	246,915,000	258,641,000	267,955,000
NIA	398,378,000	418,639,000	433,701,000
NIAMS	210,487,000	220,485,000	228,413,000
NIDCD	154,158,000	161,316,000	167,129,000
NIMH	504,709,000	526,262,000	545,223,000
NIDA	277,136,000	281,825,000	291,963,000
NIAAA	169,623,000	176,160,000	182,498,000
NINR	45,530,000	46,574,000	48,326,000
NCRR	261,776,000	270,532,000	286,394,000
NCHGR	106,134,000	128,701,000	152,010,000
FIC	14,031,000	12,825,000	13,745,000
Subtotal	8,867,523,000	9,218,929,000	9,611,557,000
NLM	102,512,000	116,899,000	135,330,000
OD	175,381,000	207,861,000	233,522,000
B&F	108,731,000	111,039,000	113,539,000
OFFICE OF AIDS RES.	1,071,457,000	1,301,045,000	1,379,052,000
TOTAL, NIH	10,325,604,000	10,955,773,000	11,473,000,000

DHHS – NATIONAL INSTITUTES OF HEALTH

FY 1995 Congressional Justification
(Dollars in Thousands)

Institute	FY 1994 Estimate			FY 1995 President's Budget			Percent Change (FY 94 to FY 95)		
	ICD Estimate	AIDS Distribution	ICD Estimate Including AIDS	ICD Estimate	Proposed AIDS Distribution	ICD Estimate Including AIDS	Before AIDS Distribution	AIDS Distribution	After AIDS Distribution
NCI	$1,868,810	($213,457)	($2,082,267)	$1,967,709	($222,712)	($2,190,421)	5.3%	(4.3%)	(5.2%)
NHLBI	1,222,903	(54,977)	(1,277,880)	1,266,961	(57,910)	(1,324,871)	3.6	(5.3)	(3.7)
NIDR	158,089	(11,431)	(169,520)	163,776	(12,097)	(175,873)	3.6	(5.8)	(3.7)
NIDDK	705,616	(10,438)	(716,054)	731,500	(11,047)	(742,547)	3.7	(5.8)	(3.7)
NINDS	608,545	(22,105)	(630,650)	630,443	(23,291)	(653,734)	3.6	(5.4)	(3.7)
NIAID	520,792	(544,791)	(1,065,583)	542,864	(578,109)	(1,120,973)	4.2	(6.1)	(5.2)
NIGMS	851,566	(23,945)	(875,511)	882,189	(25,409)	(907,598)	3.6	(6.1)	(3.7)
NICHD	498,769	(56,426)	(555,195)	516,736	(64,155)	(580,891)	3.6	(13.7)	(4.6)
NEI	281,879	(8,381)	(290,260)	292,022	(8,870)	(300,892)	3.6	(5.8)	(3.7)
NIEHS	258,641	(5,608)	(264,249)	267,955	(5,903)	(273,858)	3.6	(5.3)	(3.6)
NIA	418,639	(1,664)	(420,303)	433,701	(1,723)	(435,424)	3.6	(3.5)	(3.6)
NIAMS	220,485	(2,795)	(223,280)	228,413	(2,958)	(231,371)	3.6	(5.8)	(3.6)
NIDCD	161,316	(1,507)	(162,823)	167,129	(1,560)	(168,689)	3.6	(3.5)	(3.6)
NIMH	526,262	(87,182)	(613,444)	545,223	(92,704)	(637,927)	3.6	(6.3)	(4.0)
NIDA	281,825	(143,376)	(425,201)	291,963	(151,733)	(443,696)	3.6	(5.8)	(4.3)
NIAAA	176,160	(9,457)	(185,617)	182,498	(10,000)	(192,498)	3.6	(5.7)	(3.7)
NINR	46,574	(4,444)	(51,018)	48,326	(4,702)	(53,028)	3.8	(5.8)	(3.9)
NCRR	270,532	(61,383)	(331,915)	286,394	(64,960)	(351,354)	5.9	(5.8)	(5.9)
NCHGR	128,701	– – –	(128,701)	152,010	– – –	(152,010)	18.1	– – –	(18.1)
FIC	12,825	(8,852)	(21,677)	13,745	(9,357)	(23,102)	7.2	(5.7)	(6.6)
Subtotal	9,218,929	(1,272,219)	(10,491,148)	9,611,557	(1,349,200)	(10,960,757)	4.3	(6.1)	(4.5)
NLM	116,899	(3,082)	(119,981)	135,330	(3,191)	(138,521)	15.8	(3.5)	(15.5)
OD	207,861	– – –	(207,861)	233,522	– – –	(233,522)	12.3	– – –	(12.3)
B&F	111,039	– – –	(111,039)	113,539	– – –	(113,539)	2.3	– – –	(2.3)
OFFICE OF AIDS RES.	1,301,045	(25,744)	(25,744)	1,379,052	(26,661)	(26,661)	6.0	(3.6)	(3.6)
TOTAL, NIH	10,955,773	(1,301,045)	(10,955,773)	11,473,000	(1,379,052)	(11,473,000)	4.7	(6.0)	(4.7)

DHHS–NATIONAL INSTITUTES OF HEALTH
1995 Congressional Justification
Summary by Mechanism

INCLUDES AIDS	FY 1993 Budget Authority		FY 1994 Estimate		FY 1995 President's Budget	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	17828	$4,284,796,000	17807	$4,466,704,000	16598	$4,416,754,000
Admin. supp.	(1053)	52,192,000	(803)	39,622,000	(803)	41,497,000
Competing	6177	1,363,378,000	6203	1,450,604,000	7292	1,752,015,000
Subtotal, RPGs	24005	5,700,366,000	24010	5,956,930,000	23890	6,210,266,000
Research Ctrs:						
Spec/comp	641	672,921,000	671	727,399,000	674	772,798,000
GCRC	75	124,554,000	75	131,413,000	75	137,439,000
Biotech.	57	39,492,000	58	41,157,000	62	45,265,000
CM/BMM	42	55,217,000	37	56,197,000	37	58,186,000
RCMI	18	25,904,000	18	26,910,000	18	28,253,000
Subtotal, Centers	833	918,088,000	859	983,076,000	866	1,041,941,000
Other Research:						
Careers	1896	161,300,000	2053	176,270,000	2053	183,046,000
Clin. Ed.	78	7,815,000	73	7,904,000	80	8,904,000
Coop. Cl.	399	151,160,000	483	158,884,000	496	168,501,000
BRS	46	17,512,000	46	17,853,000	50	18,853,000
MBRS	98	44,464,000	98	47,256,000	103	49,516,000
Other	1389	109,064,000	1559	117,707,000	1677	124,871,000
Subtotal, Other	3906	491,315,000	4312	525,874,000	4459	553,691,000
Total Res. Grants	28744	7,109,769,000	29181	7,465,880,000	29215	7,805,898,000
Training						
Individual	2271	55,913,000	2356	61,394,000	2352	62,479,000
Institutional	12020	294,891,000	12032	312,000,000	11989	316,102,000
Total Training	14291	350,804,000	14388	373,394,000	14341	378,581,000
R & D Contracts	1312	694,908,000	1418	770,755,000	1466	810,551,000
Intramural Research		1,161,255,000		1,211,428,000		1,242,572,000
Res. Mgmt and Support		493,565,000		498,433,000		506,517,000
Cancer Control		105,293,000		145,759,000		197,138,000
Construction		7,528,000		25,499,000		19,500,000
Total, ICDs		9,923,122,000		10,491,148,000		10,960,757,000
Library of Medicine		103,613,000		119,981,000		138,521,000
Office of the Director		190,138,000		233,605,000		260,183,000
Buildings and Facilities		108,731,000		111,039,000		113,539,000
Total, NIH		10,325,604,000		10,955,773,000		11,473,000,000
AIDS		(1,071,457,000)		(1,301,045,000)		(1,379,052,000)
Clinical Trials		(1,025,176,000)		(1,149,224,000)		(1,178,167,000)

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DHHS–NATIONAL INSTITUTES OF HEALTH
1995 Congressional Justification
Summary by Mechanism

EXCLUDES AIDS

	FY 1993 Budget Authority		FY 1994 Estimate		FY 1995 President's Budget	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	16928	$3,969,980,000	16783	$4,088,030,000	15418	$3,938,454,000
Admin. supp.	(991)	44,147,000	(791)	38,621,000	(791)	40,455,000
Competing	5676	1,197,471,000	5605	1,260,238,000	6879	1,616,100,000
Subtot.,RPGs	22604	5,211,598,000	22388	5,386,889,000	22297	5,595,009,000
Research Ctrs:						
Spec/comp	610	623,557,000	637	666,941,000	640	708,871,000
GCRC	75	100,226,000	75	101,788,000	75	105,982,000
Biotech.	57	38,787,000	58	40,303,000	62	44,311,000
CM/BMM	31	35,926,000	26	33,704,000	26	34,585,000
RCMI	18	21,253,000	18	21,513,000	18	22,586,000
Subtot., Centers	791	819,749,000	814	864,249,000	821	916,335,000
Other Research:						
Careers	1833	155,682,000	1973	168,815,000	1974	175,445,000
Clin. Ed.	78	7,815,000	73	7,904,000	80	8,904,000
Coop. Cl.	382	138,542,000	467	145,141,000	480	153,621,000
BRS	46	17,221,000	46	17,194,000	50	18,194,000
MBRS	98	44,073,000	98	46,849,000	103	49,088,000
Other	1293	96,655,000	1449	98,382,000	1566	106,894,000
Subtotal, Other	3730	459,988,000	4106	484,285,000	4253	512,146,000
Total Res. Grants	27125	6,491,335,000	27308	6,735,423,000	27371	7,023,490,000
Training						
Individual	2207	54,415,000	2259	58,738,000	2259	59,775,000
Institutional	11455	281,565,000	11397	295,190,000	11354	299,024,000
Total Training	13662	335,980,000	13656	353,928,000	13613	358,799,000
R & D Contracts	1048	488,369,000	1081	500,933,000	1113	521,997,000
Intramural Research		995,776,000		1,017,497,000		1,044,175,000
Res. Mgmt and Support		443,242,000		439,890,000		446,458,000
Cancer Control		105,293,000		145,759,000		197,138,000
Construction		7,528,000		25,499,000		19,500,000
Total, ICDs		8,867,523,000		9,218,929,000		9,611,557,000
Library of Medicine		102,512,000		116,899,000		135,330,000
Office of the Director		175,381,000		207,861,000		233,522,000
Buildings and Facilities		108,731,000		111,039,000		113,539,000
Total, NIH		9,254,147,000		9,654,728,000		10,093,948,000

DHHS–NATIONAL INSTITUTES OF HEALTH
1995 Congressional Justification
Summary by Mechanism

AIDS ONLY	FY 1993 Budget Authority		FY 1994 Estimate		FY 1995 President's Budget	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	900	$314,816,000	1024	$378,674,000	1180	$478,300,000
Admin. supp.	(62)	8,045,000	(12)	1,001,000	(12)	1,042,000
Competing	501	165,907,000	598	190,366,000	413	135,915,000
Subtot.,RPGs	1401	488,768,000	1622	570,041,000	1593	615,257,000
Research Ctrs:						
Spec/comp	31	49,364,000	34	60,458,000	34	63,927,000
GCRC	0	24,328,000	0	29,625,000	0	31,457,000
Biotech.	0	705,000	0	854,000	0	954,000
CM/BMM	11	19,291,000	11	22,493,000	11	23,601,000
RCMI	0	4,651,000	0	5,397,000	0	5,667,000
Subtot., Centers	42	98,339,000	45	118,827,000	45	125,606,000
Other Research:						
Careers	63	5,618,000	80	7,455,000	79	7,601,000
Clin. Ed.	0	0	0	0	0	0
Coop. Cl.	17	12,618,000	16	13,743,000	16	14,880,000
BRS	0	291,000	0	659,000	0	659,000
MBRS	0	391,000	0	407,000	0	428,000
Other	96	12,409,000	110	19,325,000	111	17,977,000
Subtotal, Other	176	31,327,000	206	41,589,000	206	41,545,000
Total Res. Grants	1619	618,434,000	1873	730,457,000	1844	782,408,000
Training						
Individual	64	1,498,000	97	2,656,000	97	2,704,000
Institutional	565	13,326,000	635	16,810,000	635	17,078,000
Total Training	629	14,824,000	732	19,466,000	732	19,782,000
R & D Contracts	264	206,539,000	337	269,822,000	353	288,554,000
Intramural Research		165,479,000		193,931,000		198,397,000
Res. Mgmt and Support		50,323,000		58,543,000		60,059,000
Cancer Control		0		0		0
Construction		0		0		0
Total, ICDs		1,055,599,000		1,272,219,000		1,349,200,000
Library of Medicine		1,101,000		3,082,000		3,191,000
Office of the Director		14,757,000		25,744,000		26,661,000
Buildings and Facilities		0		0		0
Total, NIH		1,071,457,000		1,301,045,000		1,379,052,000

DHHS–NATIONAL INSTITUTES OF HEALTH
APPROPRIATIONS HISTORY

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1981	$3,512,320,000	$3,572,427,000	$3,564,765,000	$3,569,406,000 2/
1982	3,310,985,000 3/	3,834,958,000	3,818,710,000	3,641,875,000 4/
1983	3,748,771,000	4,013,450,000	4,028,591,000	4,023,969,000 5/
1984	4,091,958,000	4,314,501,000 6/	4,322,912,000 6/	4,493,588,000 7/
1985	4,566,453,000	4,834,343,000 8/	5,170,203,000	5,149,459,000
1986	4,852,680,000	5,247,836,000 9/	5,463,658,000	5,498,454,000
1986 Sequester				(236,243,000)
1987	4,936,157,000 10/	6,152,775,000	6,080,875,000	6,182,910,000
1988	8,260,277,000 11/	7,036,285,000 12/	6,408,176,000	6,666,693,000
1989	6,535,207,000 13/	6,862,495,000 14/	7,199,298,000	7,152,207,000 14/
1990	6,776,727,000 16/	7,678,625,000 17/	7,713,064,000 17/	7,672,922,000 18/
1990 Sequester				(96,570,000)
1991	7,929,686,000	8,317,654,000 19/	8,347,085,000	8,276,739,000 20/
1991 Sequester				(107,000)
1992	8,774,886,000	8,824,886,000	8,978,133,000	8,921,687,000 21/
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 22/
1994	10,667,984,000	10,936,652,000	10,956,389,000	10,955,773,000
1995	11,473,000,000 23/			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Authority was a Continuing Resolution; reflects a rescission of $47,041,000 authorized under P.L. 97–12.

3/ September budget; original request was $3,762,483,000.

4/ Continuing resolution was the lower of the House or Senate Allowance less a 4% reduction.

5/ Authority was a Continuing Resolution.

6/ Excludes $166,368,000 not considered.

7/ Includes $175,838,000 authorized under a Continuing Resolution.

8/ Includes $237,435,000 for NRSA training, not considered.

9/ Excludes $217,943,000 for NRSA training, not considered.

10/ Reflects transfer of AIDS research activities to OASH. The House allowance consolidated AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation distributed the funding among the Institutes.

11/ Includes proposed advanced appropriation of $2,726,000 for outyear cost of competing RPGs in 1988.

12/ The House allowance consolidated AIDS funding in OASH.

13/ The 1989 request excludes funds for AIDS, proposed for consolidation in OASH.

14/ Excludes $249,464,000 not considered.

15/ Includes real transfer of $7,443 to OASH for AZT

16/ The 1990 request excludes funds for AIDS, proposed for consolidation in OASH.

17/ Includes $752,670,000 for AIDS research.

18/ Reflects reductions of $10,000,000 for extramural salary cap savings, $4,000,000 for procurement reform and a $10,428,000 reduction in salaries & expense.

19/ Excludes $304,814,000 not considered.

20/ Reflects enacted administrative reduction of $29,909,000 for salaries and expense and $205,134,000 associated with the 2.41 percent across the board reduction.

21/ Reflects enacted administrative reduction of $69,603,000 for salaries and expense a travel reduction of $5,984,000, and a rescission of $13,131,000.

22/ Reflects enacted administrative reductions of an across the board .8 percent for $83,571,000, $34,857,000 for salaries and expenses and a consultant services reduction of $1,342,000. All columns adjusted to include transfer from ADAMHA.

23/ Includes $1,379,052,000 for HIV Research proposed for consolidation in the NIH Office of AIDS Research.

DHHS–NATIONAL INSTITUTES OF HEALTH
HISTORY OF OBLIGATIONS BY TOTAL MECHANISM
(Dollars in Thousands)

INCLUDES AIDS

Mechanism	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
Research Project Grants	$2,951,558	$3,121,780	$3,729,454	$4,028,722	$4,405,645	$4,625,833	$5,046,134	$5,459,375	$5,700,366	$5,956,930	$6,210,266
Research Centers	496,131	493,660	561,954	615,668	657,767	702,215	796,007	891,772	918,088	983,076	1,041,941
Other Research	331,983	324,430	374,158	394,980	441,349	493,993	546,136	561,400	491,315	525,874	553,691
Subtotal Research Grants	3,779,672	3,939,870	4,665,566	5,039,370	5,504,761	5,822,041	6,388,277	6,912,547	7,109,769	7,465,880	7,805,898
Research Training	238,465	232,873	256,407	262,941	283,015	318,896	342,260	348,018	350,804	373,394	378,581
R & D Contracts	383,263	358,258	503,586	532,446	583,496	630,487	664,698	705,821	694,908	770,755	810,551
Intramural Research	639,451	640,177	748,637	805,417	882,417	975,871	1,048,834	1,132,166	1,161,255	1,211,428	1,242,572
Res. Mgt. & Support	273,098	256,909	289,925	323,499	356,867	405,358	434,706	484,327	493,565	498,433	506,517
Cancer Control	63,794	61,372	67,457	69,682	74,100	75,433	85,390	107,569	105,293	145,759	197,138
Construction	13,100	9,439	9,550	0	31,345	16,322	7,349	12,000	7,528	25,499	19,500
Subtotal ICDs	5,390,843	5,498,898	6,541,128	7,033,355	7,716,001	8,244,408	8,971,514	9,702,448	9,923,122	10,491,148	10,960,757
Library of Medicine	55,184	55,206	61,675	67,700	78,798	81,683	91,182	102,937	103,613	119,981	138,521
Office of the Director	35,396	114,712	56,917	66,875	74,371	111,729	98,153	143,542	190,138	233,605	260,183
Buildings & Facilities	15,675	19,933	25,786	19,029	24,416	67,436	57,091	61,441	108,731	111,039	113,539
All Other	515,132	585,092	595,543	618,266	724,379	846,596	885,301	988,889	1,006,618	1,161,757	1,282,572
Total, NIH	5,497,098	5,688,749	6,685,506	7,186,959	7,893,586	8,505,256	9,217,940	10,010,368	10,325,604	10,955,773	11,473,000

DHHS–NATIONAL INSTITUTES OF HEALTH
PERCENTAGE SHARE OF NIH TOTAL OBLIGATION BY MECHANISM

INCLUDES AIDS

PERCENT TO TOTAL

Mechanism	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
Research Project Grants	53.7%	54.9%	55.8%	56.1%	55.8%	54.4%	54.7%	54.5%	55.2%	54.4%	54.1%
Research Centers	9.0%	8.7%	8.4%	8.6%	8.3%	8.3%	8.6%	8.9%	8.9%	9.0%	9.1%
Other Research	6.0%	5.7%	5.6%	5.5%	5.6%	5.8%	5.9%	5.6%	4.8%	4.8%	4.8%
Subtotal Research Grants	68.8%	69.3%	69.8%	70.1%	69.7%	68.5%	69.3%	69.1%	68.9%	68.1%	68.0%
Research Training	4.3%	4.1%	3.8%	3.7%	3.6%	3.7%	3.7%	3.5%	3.4%	3.4%	3.3%
R & D Contracts	7.0%	6.3%	7.5%	7.4%	7.4%	7.4%	7.2%	7.1%	6.7%	7.0%	7.1%
Intramural Research	11.6%	11.3%	11.2%	11.2%	11.2%	11.5%	11.4%	11.3%	11.2%	11.1%	10.8%
Res. Mgt. & Support	5.0%	4.5%	4.3%	4.5%	4.5%	4.8%	4.7%	4.8%	4.8%	4.5%	4.4%
Cancer Control	1.2%	1.1%	1.0%	1.0%	0.9%	0.9%	0.9%	1.1%	1.0%	1.3%	1.7%
Construction	0.2%	0.2%	0.1%	0.0%	0.4%	0.2%	0.1%	0.1%	0.1%	0.2%	0.2%
Subtotal ICDs	98.1%	96.7%	97.8%	97.9%	97.8%	96.9%	97.3%	96.9%	96.1%	95.8%	95.5%
Library of Medicine	1.0%	1.0%	0.9%	0.9%	1.0%	1.0%	1.0%	1.0%	1.0%	1.1%	1.2%
Office of the Director	0.6%	2.0%	0.9%	0.9%	0.9%	1.3%	1.1%	1.4%	1.8%	2.1%	2.3%
Buildings & Facilities	0.3%	0.4%	0.4%	0.3%	0.3%	0.8%	0.6%	0.5%	1.1%	1.0%	1.0%
All Other	9.4%	10.3%	8.9%	8.6%	9.2%	10.0%	9.6%	9.9%	9.7%	10.6%	11.2%
Total, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

DHHS–NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985–1995

INCLUDES AIDS

(Dollars in Thousands)

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	$1,177,853	$1,210,284	$1,402,790	$1,468,435	$1,570,342	$1,644,330	$1,712,669	$1,947,571	$1,978,420	$2,082,267	$2,190,421
NHLBI	803,810	821,901	929,981	965,283	1,045,508	1,070,683	1,125,915	1,190,070	1,214,740	1,277,880	1,324,871
NIDR	100,414	98,755	117,926	126,216	130,689	135,432	148,691	158,900	161,142	169,520	175,873
NIDDK	539,499	436,037	510,880	534,359	559,274	579,984	615,262	661,446	680,672	716,054	742,547
NINDS	396,170	414,406	490,136	458,792	471,632	489,348	542,313	580,790	599,488	630,650	653,734
NIAID	370,047	367,142	545,433	638,521	740,239	831,181	906,003	960,082	984,227	1,065,583	1,120,973
NIGMS	480,975	493,535	570,867	627,465	682,134	680,305	761,231	814,297	832,235	875,511	907,598
NICHD	312,578	308,211	366,651	396,584	425,268	441,955	478,947	518,577	527,767	555,195	580,891
NEI	181,298	186,343	216,528	224,835	230,999	236,456	253,354	269,766	275,917	290,260	300,892
NIEHS	194,486	188,819	209,251	215,439	223,309	228,725	240,606	251,484	251,187	264,249	273,858
NIA	142,968	150,910	177,461	194,548	222,545	238,927	323,791	382,882	399,531	420,303	435,424
NIAMS	---	111,336	138,675	147,543	159,886	168,538	193,449	203,516	212,247	223,280	231,371
NIDCD	---	---	---	75,691	94,275	117,283	134,957	148,748	154,776	162,823	168,689
NIMH	232,734	242,066	287,804	327,514	384,928	440,222	511,967	560,285	583,142	613,444	637,927
NIDA	81,130	83,311	139,307	156,252	228,131	329,560	383,656	399,100	404,183	425,201	443,696
NIAAA	61,677	66,395	83,357	92,763	120,051	149,194	158,141	171,481	176,446	185,617	192,498
NINR	---	16,193	19,924	23,361	29,118	33,508	39,892	44,925	48,496	51,018	53,028
NCRR	303,641	292,388	322,781	344,150	381,934	353,771	335,776	314,198	312,657	331,915	351,354
NCHGR	---	---	---	---	---	59,527	87,389	104,756	106,134	128,701	152,010
FIC	11,563	10,866	11,376	15,604	15,739	15,479	17,505	19,574	19,715	21,677	23,102
Subtotal, ICDs	5,390,843	5,498,898	6,541,128	7,033,355	7,716,001	8,244,408	8,971,514	9,702,448	9,923,122	10,491,148	10,960,757
NLM	55,184	55,206	61,675	67,700	78,798	81,683	91,182	102,937	103,613	119,981	138,521
OD	35,396	114,712	56,917	66,875	74,371	111,729	98,153	143,542	190,138	233,605	260,183
B & F	15,675	19,933	25,786	19,029	24,416	67,436	57,091	61,441	108,731	111,039	113,539
TOTAL, NIH	5,497,098	5,688,749	6,685,506	7,186,959	7,893,586	8,505,256	9,217,940	10,010,368	10,325,604	10,955,773	11,473,000

DHHS–NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985–1995

INCLUDES AIDS

PERCENT TO TOTAL

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	21.4%	21.3%	21.0%	20.4%	19.9%	19.3%	18.6%	19.5%	19.2%	19.0%	19.1%
NHLBI	14.6%	14.4%	13.9%	13.4%	13.2%	12.6%	12.2%	11.9%	11.8%	11.7%	11.5%
NIDR	1.8%	1.7%	1.8%	1.8%	1.7%	1.6%	1.6%	1.6%	1.6%	1.5%	1.5%
NIDDK	9.8%	7.7%	7.6%	7.4%	7.1%	6.8%	6.7%	6.6%	6.6%	6.5%	6.5%
NINDS	7.2%	7.3%	7.3%	6.4%	6.0%	5.8%	5.9%	5.8%	5.8%	5.8%	5.7%
NIAID	6.7%	6.5%	8.2%	8.9%	9.4%	9.8%	9.8%	9.6%	9.5%	9.7%	9.8%
NIGMS	8.7%	8.7%	8.5%	8.7%	8.6%	8.0%	8.3%	8.1%	8.1%	8.0%	7.9%
NICHD	5.7%	5.4%	5.5%	5.5%	5.4%	5.2%	5.2%	5.2%	5.1%	5.1%	5.1%
NEI	3.3%	3.3%	3.2%	3.1%	2.9%	2.8%	2.7%	2.7%	2.7%	2.6%	2.6%
NIEHS	3.5%	3.3%	3.1%	3.0%	2.8%	2.7%	2.6%	2.5%	2.4%	2.4%	2.4%
NIA	2.6%	2.7%	2.7%	2.7%	2.8%	2.8%	3.5%	3.8%	3.9%	3.8%	3.8%
NIAMS	0.0%	2.0%	2.1%	2.1%	2.0%	2.0%	2.1%	2.0%	2.1%	2.0%	2.0%
NIDCD	0.0%	0.0%	0.0%	1.1%	1.2%	1.4%	1.5%	1.5%	1.5%	1.5%	1.5%
NIMH	4.2%	4.3%	4.3%	4.6%	4.9%	5.2%	5.6%	5.6%	5.6%	5.6%	5.6%
NIDA	1.5%	1.5%	2.1%	2.2%	2.9%	3.9%	4.2%	4.0%	3.9%	3.9%	3.9%
NIAAA	1.1%	1.2%	1.2%	1.3%	1.5%	1.8%	1.7%	1.7%	1.7%	1.7%	1.7%
NINR	0.0%	0.3%	0.3%	0.3%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.5%
NCRR	5.5%	5.1%	4.8%	4.8%	4.8%	4.2%	3.6%	3.1%	3.0%	3.0%	3.1%
NCHGR	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	0.9%	1.0%	1.0%	1.2%	1.3%
FIC	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Subtotal, ICDs	98.1%	96.7%	97.8%	97.9%	97.8%	96.9%	97.3%	96.9%	96.1%	95.8%	95.5%
NLM	1.0%	1.0%	0.9%	0.9%	1.0%	1.0%	1.0%	1.0%	1.0%	1.1%	1.2%
OD	0.6%	2.0%	0.9%	0.9%	0.9%	1.3%	1.1%	1.4%	1.8%	2.1%	2.3%
B & F	0.3%	0.4%	0.4%	0.3%	0.3%	0.8%	0.6%	0.6%	1.1%	1.0%	1.0%
TOTAL, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

DHHS–NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985–1995

(Dollars in Thousands)

EXCLUDES AIDS

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	$1,150,979	$1,165,234	$1,339,035	$1,378,491	$1,448,095	$1,494,026	$1,551,800	$1,781,903	$1,805,391	$1,868,810	$1,967,709
NHLBI	794,487	806,433	912,737	940,398	1,007,448	1,028,599	1,079,509	1,143,864	1,166,682	1,222,903	1,266,961
NIDR	100,317	97,043	114,679	122,366	126,769	130,770	142,477	150,746	152,767	158,089	163,776
NIDDK	539,499	436,037	510,385	531,029	555,717	574,678	608,972	654,274	674,226	705,616	731,500
NINDS	395,002	412,971	486,451	446,450	458,563	473,190	525,662	563,198	581,072	608,545	630,443
NIAID	346,774	303,866	399,673	415,223	428,962	438,098	475,063	511,292	524,529	520,792	542,864
NIGMS	480,975	493,535	565,447	619,741	671,304	665,691	745,643	798,197	815,385	851,566	882,189
NICHD	312,578	306,811	361,889	379,431	402,831	415,206	446,338	483,848	488,960	498,769	516,736
NEI	181,098	186,247	216,275	221,005	226,171	230,923	247,674	263,864	269,634	281,879	292,022
NIEHS	194,486	188,819	209,035	211,543	219,171	224,467	236,092	247,268	246,915	258,641	267,955
NIA	142,968	150,910	177,277	194,187	222,102	238,068	322,806	381,810	398,378	418,639	433,701
NIAMS	0	111,336	138,575	146,982	159,213	167,300	191,816	201,822	210,487	220,485	228,413
NIDCD	0	0	0	75,691	94,275	117,283	134,462	148,265	154,158	161,316	167,129
NIMH	230,932	237,006	277,334	296,326	336,555	376,891	439,247	484,145	504,709	526,262	545,223
NIDA	80,452	76,382	119,077	122,404	167,307	236,925	260,968	273,831	277,136	281,825	291,963
NIAAA	61,677	66,395	80,987	87,970	113,921	141,214	150,145	163,491	169,623	176,160	182,498
NINR	0	16,193	19,924	22,759	28,416	32,521	37,347	42,215	45,530	46,574	48,326
NCRR	300,839	286,231	311,754	315,867	314,318	307,624	288,347	264,147	261,776	270,532	286,394
NCHGR	0	0	0	0	0	59,527	87,389	104,756	106,134	128,701	152,010
FIC	11,563	10,866	11,376	11,099	11,120	10,581	12,154	13,981	14,031	12,825	13,745
Subtotal, ICDs	5,324,626	5,352,315	6,251,910	6,538,962	6,992,258	7,363,582	7,983,911	8,676,917	8,867,523	9,218,929	9,611,557
NLM	55,184	55,206	61,675	67,700	78,778	81,190	90,663	101,880	102,512	116,899	135,330
OD	35,396	114,639	52,158	61,239	61,506	111,729	86,416	128,429	175,381	207,861	233,522
B&F	15,675	19,933	25,786	18,659	18,644	54,556	52,125	53,683	108,731	111,039	113,539
TOTAL, NIH	5,430,881	5,542,093	6,391,529	6,686,560	7,151,186	7,611,057	8,213,115	8,960,909	9,254,147	9,654,728	10,093,948

DHHS–NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985–1995

EXCLUDES AIDS

PERCENT TO TOTAL

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	21.2%	21.0%	21.0%	20.6%	20.2%	19.6%	18.9%	19.9%	19.5%	19.4%	19.5%
NHLBI	14.6%	14.6%	14.3%	14.1%	14.1%	13.5%	13.1%	12.8%	12.6%	12.7%	12.6%
NIDR	1.8%	1.8%	1.8%	1.8%	1.8%	1.7%	1.7%	1.7%	1.7%	1.6%	1.6%
NIDDK	9.9%	7.9%	8.0%	7.9%	7.8%	7.6%	7.4%	7.3%	7.3%	7.3%	7.2%
NINDS	7.3%	7.5%	7.6%	6.7%	6.4%	6.2%	6.4%	6.3%	6.3%	6.3%	6.2%
NIAID	6.4%	5.5%	6.3%	6.2%	6.0%	5.8%	5.8%	5.7%	5.7%	5.4%	5.4%
NIGMS	8.9%	8.9%	8.8%	9.3%	9.4%	8.7%	9.1%	8.9%	8.8%	8.8%	8.7%
NICHD	5.8%	5.5%	5.7%	5.7%	5.6%	5.5%	5.4%	5.4%	5.3%	5.2%	5.1%
NEI	3.3%	3.4%	3.4%	3.3%	3.2%	3.0%	3.0%	2.9%	2.9%	2.9%	2.9%
NIEHS	3.6%	3.4%	3.3%	3.2%	3.1%	2.9%	2.9%	2.8%	2.7%	2.7%	2.7%
NIA	2.6%	2.7%	2.8%	2.9%	3.1%	3.1%	3.9%	4.3%	4.3%	4.3%	4.3%
NIAMS	0.0%	2.0%	2.2%	2.2%	2.2%	2.2%	2.3%	2.3%	2.3%	2.3%	2.3%
NIDCD	0.0%	0.0%	0.0%	1.1%	1.3%	1.5%	1.6%	1.7%	1.7%	1.7%	1.7%
NIMH	4.3%	4.3%	4.3%	4.4%	4.7%	5.0%	5.3%	5.4%	5.5%	5.5%	5.4%
NIDA	1.5%	1.4%	1.9%	1.8%	2.3%	3.1%	3.2%	3.1%	3.0%	2.9%	2.9%
NIAAA	1.1%	1.2%	1.3%	1.3%	1.6%	1.9%	1.8%	1.8%	1.8%	1.8%	1.8%
NINR	0.0%	0.3%	0.3%	0.3%	0.4%	0.4%	0.5%	0.5%	0.5%	0.5%	0.5%
NCRR	5.5%	5.2%	4.9%	4.7%	4.4%	4.0%	3.5%	2.9%	2.8%	2.8%	2.8%
NCHGR	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%	1.1%	1.2%	1.1%	1.3%	1.5%
FIC	0.2%	0.2%	0.2%	0.2%	0.2%	0.1%	0.1%	0.2%	0.2%	0.1%	0.1%
Subtotal, ICDs	98.0%	96.6%	97.8%	97.8%	97.8%	96.7%	97.2%	96.8%	95.8%	95.5%	95.2%
NLM	1.0%	1.0%	1.0%	1.0%	1.1%	1.1%	1.1%	1.1%	1.1%	1.2%	1.3%
OD	0.7%	2.1%	0.8%	0.9%	0.9%	1.5%	1.1%	1.4%	1.9%	2.2%	2.3%
B&F	0.3%	0.4%	0.4%	0.3%	0.3%	0.7%	0.6%	0.6%	1.2%	1.2%	1.1%
TOTAL, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

DHHS–NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985–1995

AIDS ONLY

(Dollars in Thousands)

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	$26,874	$45,050	$63,755	$89,944	$122,247	$150,304	$160,869	$165,668	$173,029	$213,457	$222,712
NHLBI	9,323	15,468	17,244	24,885	38,088	42,056	46,406	46,206	48,058	54,977	57,910
NIDR	97	1,712	3,247	3,850	3,920	4,662	6,214	8,154	8,375	11,431	12,097
NIDDK	0	0	495	3,330	3,557	5,306	6,290	7,172	6,446	10,438	11,047
NINDS	1,168	1,435	3,685	12,342	13,069	16,158	16,651	17,592	18,416	22,105	23,291
NIAID	23,273	63,276	145,760	223,298	311,277	393,083	430,940	448,940	459,698	544,791	578,109
NIGMS	0	0	5,420	7,724	10,830	14,614	15,588	16,100	16,850	23,945	25,409
NICHD	0	1,400	4,762	17,153	22,437	26,749	32,609	34,729	38,807	56,426	64,155
NEI	200	96	253	3,830	4,828	5,533	5,680	5,902	6,283	8,381	8,870
NIEHS	0	0	216	3,896	4,138	4,258	4,514	4,216	4,272	5,608	5,903
NIA	0	0	184	361	443	859	985	1,072	1,153	1,664	1,723
NIAMS	0	0	100	561	673	1,238	1,633	1,694	1,760	2,795	2,958
NIDCD	0	0	0	0	0	0	495	483	618	1,507	1,560
NIMH	1,802	5,060	10,470	31,188	48,373	63,331	72,720	76,140	78,433	87,182	92,704
NIDA	678	6,929	20,230	33,848	60,824	92,635	122,688	125,269	127,047	143,376	151,733
NIAAA	0	0	2,370	4,793	6,130	7,980	7,996	7,990	6,823	9,457	10,000
NINR	0	0	0	602	702	987	2,545	2,710	2,966	4,444	4,702
NCRR	2,802	6,157	11,027	28,283	67,616	46,147	47,429	50,051	50,881	61,383	64,960
NCHGR	0	0	0	0	0	0	0	0	0	0	0
FIC	0	0	0	4,505	4,619	4,898	5,351	5,593	5,684	8,852	9,357
Subtotal, ICDs	66,217	146,583	289,218	494,393	723,771	880,798	987,603	1,025,681	1,055,599	1,272,219	1,349,200
NLM	0	0	0	0	20	493	519	1,057	1,101	3,082	3,191
OD	0	73	4,759	5,636	12,865	10,284	11,737	15,113	14,757	25,744	26,661
B&F	0	0	0	370	5,772	12,880	4,966	7,758	0	0	0
TOTAL, NIH	66,217	146,656	293,977	500,399	742,428	904,455	1,004,825	1,049,609	1,071,457	1,301,045	1,379,052

DHHS—NATIONAL INSTITUTES OF HEALTH

HISTORY OF OBLIGATIONS, 1985–1995

AIDS ONLY

PERCENT TO TOTAL

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	40.6%	30.7%	21.7%	18.0%	16.5%	16.6%	16.0%	15.8%	16.1%	16.4%	16.1%
NHLBI	14.1%	10.5%	5.9%	5.0%	5.1%	4.6%	4.6%	4.4%	4.5%	4.2%	4.2%
NIDR	0.1%	1.2%	1.1%	0.8%	0.5%	0.5%	0.6%	0.8%	0.8%	0.9%	0.9%
NIDDK	0.0%	0.0%	0.2%	0.7%	0.5%	0.6%	0.6%	0.7%	0.6%	0.8%	0.8%
NINDS	1.8%	1.0%	1.3%	2.5%	1.8%	1.8%	1.7%	1.7%	1.7%	1.7%	1.7%
NIAID	35.1%	43.1%	49.6%	44.6%	41.9%	43.5%	42.9%	42.8%	42.9%	41.9%	41.9%
NIGMS	0.0%	0.0%	1.8%	1.5%	1.5%	1.6%	1.6%	1.5%	1.6%	1.8%	1.8%
NICHD	0.0%	1.0%	1.6%	3.4%	3.0%	3.0%	3.2%	3.3%	3.6%	4.3%	4.7%
NEI	0.3%	0.1%	0.1%	0.8%	0.7%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%
NIEHS	0.0%	0.0%	0.1%	0.8%	0.6%	0.5%	0.4%	0.4%	0.4%	0.4%	0.4%
NIA	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
NIAMS	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%
NIDCD	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%
NIMH	2.7%	3.5%	3.6%	6.2%	6.5%	7.0%	7.2%	7.3%	7.3%	6.7%	6.7%
NIDA	1.0%	4.7%	6.9%	6.8%	8.2%	10.2%	12.2%	11.9%	11.9%	11.0%	11.0%
NIAAA	0.0%	0.0%	0.8%	1.0%	0.8%	0.9%	0.8%	0.8%	0.6%	0.7%	0.7%
NINR	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.3%	0.3%	0.3%	0.3%	0.3%
NCRR	4.2%	4.2%	3.8%	5.7%	9.1%	5.1%	4.7%	4.8%	4.7%	4.7%	4.7%
NCHGR	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
FIC	0.0%	0.0%	0.0%	0.9%	0.6%	0.5%	0.5%	0.5%	0.5%	0.7%	0.7%
Subtotal, ICDs	100.0%	100.0%	98.4%	98.8%	97.5%	97.4%	98.3%	97.7%	98.5%	97.8%	97.8%
NLM	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%
OD	0.0%	0.0%	1.6%	1.1%	1.7%	1.1%	1.2%	1.4%	1.4%	2.0%	1.9%
B&F	0.0%	0.0%	0.0%	0.1%	0.8%	1.4%	0.5%	0.7%	0.0%	0.0%	0.0%
TOTAL, NIH	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

DHHS – NATIONAL INSTITUTES OF HEALTH

National Support for Performance of Medical and Health – Related R&D, by Source of Funds
Fiscal Years 1983 – 1993
(Dollars in Millions)

Source of Funds	FY 1983	FY 1984	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991 Estimate	FY 1992 Estimate	FY 1993 Projection
Total	$10,778	$12,155	$13,560	$14,894	$16,931	$18,996	$20,914	$23,094	$25,754	$28,718	$30,827
Government	6,117	6,883	7,669	7,924	9,028	9,725	10,628	11,418	12,429	13,626	14,017
Federal	5,399	6,087	6,791	6,895	7,847	8,431	9,163	9,791	10,602	11,727	11,978
NIH	(4,091)	(4,257)	(4,828)	(5,005)	(5,852)	(6,292)	(6,778)	(7,136)	(7,696)	(8,407)	(9,769)
State & local	718	796	878	1,028	1,182	1,294	1,465	1,628	1,828	1,900	2,040
Industry	4,205	4,765	5,352	6,188	7,104	8,433	9,405	10,717	12,234	13,870	15,562
Private nonprofit	456	507	539	782	799	838	881	959	1,091	1,222	1,248
Foundations	89	111	122	129	161	155	129	155	178	236	211
Voluntary health agencies	206	205	233	260	285	323	354	363	393	420	447
Howard Hughes Medical Inst.	54	79	51	247	183	179	197	215	250	273	268
Other	107	112	133	146	170	181	201	226	270	293	322

NOTES:

- Excludes research training and construction.
- These figures report support for the direct conduct of biomedical research. In addition, HHMI's Office of Grants and Special Programs provides support for scientific career development, which is not included here.

Source: NIH Data Book, 1993

INCLUDES AIDS

DHHS–NATIONAL INSTITUTES OF HEALTH
RESEARCH CENTERS
TOTAL AWARDS

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	58	59	60	60	56	56	57	88	79	77	82
NHLBI	60	60	60	65	64	65	65	65	68	73	73
NIDR	13	16	13	16	19	21	22	28	28	28	27
NIDDK	45	31	37	38	40	42	42	47	61	61	61
NINDS	40	38	38	29	29	30	35	42	44	46	46
NIAID	18	17	16	22	26	28	27	27	17	17	17
NIGMS	15	13	14	16	10	10	9	8	9	9	9
NICHD	43	44	44	44	46	55	64	73	75	77	78
NEI	28	29	30	29	29	30	30	29	29	29	29
NIEHS	15	15	15	16	16	17	17	18	18	20	22
NIA	12	12	14	13	18	31	40	42	50	56	57
NIAMS	0	14	23	25	26	26	26	28	28	30	30
NIDCD	0	0	0	9	9	12	18	17	15	16	16
NIMH	22	25	28	33	37	45	44	53	56	60	60
NIDA	4	8	13	18	18	20	22	24	23	32	32
NIAAA	9	9	11	10	12	14	14	14	14	14	14
NINR	0	0	0	0	4	4	7	7	7	7	7
NCRR	185	183	183	190	192	176	198	202	192	188	192
NCHGR	0	0	0	0	0	4	9	13	13	13	14
FIC	0	0	0	0	0	0	0	0	0	0	0
TOTAL	567	573	599	633	651	686	746	825	826	853	866
Average Cost per Center ($ in 1,000s)	$875.0	$861.5	$938.2	$972.6	$1,010.4	$1,023.6	$1,067.0	$1,080.9	$1,093.5	$1,152.5	$1,203.2
Percent Change in Av. Cost		–1.5%	8.9%	3.7%	3.9%	1.3%	4.2%	1.3%	1.2%	5.4%	4.4%

DHHS—NATIONAL INSTITUTES OF HEALTH
RESEARCH TRAINING

INCLUDES AIDS

Number of Full–Time Training Positions

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	1,464	1,394	1,475	1,456	1,428	1,485	1,497	1,491	1,446	1,388	1,388
NHLBI	1,709	1,633	1,666	1,655	1,628	1,519	1,567	1,640	1,557	1,590	1,590
NIDR	197	192	225	224	189	195	211	205	200	201	201
NIDDK	1,046	764	915	916	825	804	843	849	865	868	868
NINDS	623	579	653	544	546	564	503	516	504	522	522
NIAID	518	487	491	561	579	711	754	732	801	777	777
NIGMS	3,396	3,238	3,566	3,587	3,702	3,838	4,215	4,333	4,325	4,507	4,507
NICHD	702	728	736	723	640	677	723	743	767	750	750
NEI	220	232	229	252	251	258	261	262	280	261	261
NIEHS	483	446	462	480	434	481	556	467	460	456	456
NIA	227	263	313	344	387	426	418	436	456	434	434
NIAMS	0	223	242	238	219	228	215	233	218	239	239
NIDCD	0	0	0	96	105	112	142	166	189	185	185
NIMH	914	882	993	1,000	1,077	1,183	1,218	1,242	1,289	1,262	1,262
NIDA	79	79	114	114	114	174	276	297	302	313	313
NIAAA	69	71	123	129	120	147	160	141	149	178	178
NINR	0	153	167	186	219	257	269	261	233	208	208
NCRR	39	36	41	67	73	82	82	82	80	81	79
NCHGR	0	0	0	0	0	130	158	171	170	168	123
FIC	0	0	0	0	0	0	0	0	0	0	0
TOTAL	11,686	11,400	12,411	12,572	12,536	13,271	14,068	14,267	14,291	14,388	14,341
Average Cost per FTTP ($ in 1,000s)	$20.4	$20.4	$20.7	$20.9	$22.6	$24.0	$24.3	$24.4	$24.5	$26.0	$26.4
Percent Change in Av. Cost		0.1%	1.1%	1.2%	7.9%	6.4%	1.2%	0.3%	0.6%	5.7%	1.7%

DHHS–NATIONAL INSTITUTES OF HEALTH

Success Rates – Research Project Grants

INSTITUTE	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
NCI	32.0%	30.2%	34.2%	32.7%	25.0%	23.5%	27.5%	32.2%	24.6%	22%	25%
NHLBI	32.4%	31.4%	32.6%	31.4%	25.7%	24.9%	27.5%	29.2%	21.9%	27%	30%
NIDR	34.4%	33.5%	28.5%	25.4%	23.9%	21.0%	30.0%	27.1%	24.3%	31%	28%
NIDDK	31.9%	33.1%	38.0%	31.8%	26.3%	23.0%	26.8%	32.7%	22.0%	22%	23%
NINDS	33.9%	34.0%	39.4%	39.6%	31.7%	24.2%	29.9%	26.6%	25.1%	22%	25%
NIAID	33.6%	32.0%	34.1%	30.6%	30.1%	27.4%	31.0%	30.0%	29.4%	27%	30%
NIGMS	42.9%	40.1%	38.0%	38.5%	28.3%	22.0%	34.4%	35.7%	29.8%	29%	38%
NICHD	24.9%	23.9%	33.2%	24.6%	24.6%	19.3%	25.1%	26.3%	21.3%	21%	21%
NEI	46.6%	46.5%	49.5%	42.9%	42.8%	37.5%	32.8%	31.0%	32.1%	31%	26%
NIEHS	27.8%	25.7%	28.9%	28.5%	26.5%	28.3%	27.5%	28.0%	21.1%	21%	22%
NIA	27.8%	25.0%	27.7%	25.4%	23.6%	21.6%	30.4%	28.9%	23.1%	25%	26%
NIAMS	---	30.6%	28.5%	26.1%	26.4%	20.0%	31.3%	17.5%	20.9%	19%	19%
NIDCD	---	---	---	39.7%	38.2%	36.9%	30.9%	30.2%	29.3%	28%	27%
NIMH	30.4%	26.0%	33.2%	28.7%	29.2%	24.4%	27.3%	26.9%	19.5%	27%	24%
NIDA	41.1%	37.8%	48.1%	17.3%	36.7%	36.7%	31.2%	30.9%	31.8%	31%	29%
NIAAA	30.3%	30.2%	35.5%	26.9%	38.0%	34.3%	22.9%	31.3%	19.2%	30%	28%
NINR	---	22.1%	30.0%	26.9%	18.9%	16.4%	19.2%	15.4%	11.3%	10%	19%
NCRR	---	---	---	---	---	21.6%	28.8%	32.7%	28.4%	27%	22%
NCHGR	---	---	---	---	31.8%	23.3%	37.9%	21.6%	27.9%	17%	15%
FIC	---	---	---	---	---	---	---	---	---	6%	---
NIH	33.4%	32.1%	34.9%	32.4%	27.6%	24.0%	29.3%	29.6%	24.5%	25%	27%

DHHS–NATIONAL INSTITUTES OF HEALTH

Success Rates

	FY 1993 Budget Authority			FY 1994 Estimate			FY 1995 President's Budget		
INSTITUTE	AIDS	NONAIDS	TOTAL	AIDS	NONAIDS	TOTAL	AIDS	NONAIDS	TOTAL
NCI	24.6%	24.6%	24.6%	22%	22%	22%	25%	25%	25%
NHLBI	21.9%	21.9%	21.9%	27%	27%	27%	30%	30%	30%
NIDR	25.0%	24.3%	24.3%	31%	31%	31%	29%	28%	28%
NIDDK	22.5%	22.0%	22.0%	22%	22%	22%	23%	23%	23%
NINDS	28.3%	25.0%	25.1%	22%	22%	22%	25%	25%	25%
NIAID	43.5%	23.2%	29.4%	46%	20%	27%	38%	27%	30%
NIGMS	29.7%	29.8%	29.8%	29%	29%	29%	39%	38%	38%
NICHD	21.3%	21.3%	21.3%	21%	21%	21%	21%	21%	21%
NEI	32.2%	32.1%	32.1%	31%	31%	31%	26%	26%	26%
NIEHS	0.0%	21.1%	21.1%	0%	21%	21%	22%	22%	22%
NIA	0.0%	23.1%	23.1%	25%	25%	25%	26%	26%	26%
NIAMS	20.9%	20.9%	20.9%	19%	19%	19%	19%	19%	19%
NIDCD	0.0%	29.3%	29.3%	28%	28%	28%	0%	27%	27%
NIMH	16.3%	19.8%	19.5%	28%	27%	27%	22%	25%	24%
NIDA	62.7%	26.8%	31.8%	95%	20%	31%	52%	26%	29%
NIAAA	19.2%	19.2%	19.2%	30%	30%	30%	28%	28%	28%
NINR	11.3%	11.3%	11.3%	10%	10%	10%	19%	19%	19%
NCRR	28.4%	28.4%	28.4%	27%	27%	27%	22%	22%	22%
NCHGR	0.0%	27.9%	27.9%	0%	17%	17%	0%	15%	15%
FIC	0.0%	0.0%	0.0%	0%	6%	6%	0%	0%	0%
NIH	36.3%	23.8%	24.5%	37%	24%	25%	32%	27%	27%

DHHS – NATIONAL INSTITUTES OF HEALTH

STATISTICAL DATA – RESEARCH GRANTS, DIRECT AND INDIRECT COSTS AWARDED 1/
(Dollars in Thousands)

Fiscal Year	Direct Costs Awarded	Indirect Costs Awarded	Total Dollars Awarded	Percent To Total In Dollars		Percent Growth In Dollars	
				Direct	Indirect	Direct	Indirect
1977	$961,162	$359,140	$1,320,302	72.8	27.2	---	---
1978	1,112,973	416,093	1,529,066	72.8	27.2	15.8	15.9
1979	1,331,722	512,279	1,844,001	72.2	27.8	19.7	23.1
1980	1,463,768	586,306	2,050,074	71.4	28.6	9.9	14.5
1981	1,568,995	655,143	2,224,138	70.5	29.5	7.2	11.7
1982	1,610,679	689,855	2,300,534	70.0	30.0	2.7	5.3
1983	1,793,207	791,580	2,584,787	69.4	30.6	11.3	14.7
1984	2,036,639	921,627	2,958,266	68.8	31.2	13.6	16.4
1985	2,343,216	1,069,707	3,412,923	68.7	31.3	15.1	16.1
1986	2,444,946	1,119,115	3,564,061	68.6	31.4	4.3	4.6
1987	2,876,830	1,311,539	4,188,369	68.7	31.3	17.7	17.2
1988	3,124,042	1,416,716	4,540,758	68.8	31.2	8.6	8.0
1989	3,315,563	1,530,547	4,846,110	68.4	31.6	6.1	8.0
1990	3,428,392	1,599,286	5,027,678	68.2	31.8	3.4	4.5
1991	3,748,778	1,744,378	5,493,156	68.2	31.8	9.3	9.1
1992	4,169,928	1,896,215	6,066,143	68.7	31.3	11.2	8.7
1993	4,888,871	2,183,265	7,072,136	69.1	30.9	17.2	15.1
1994 Estimate	5,098,605	2,279,984	7,378,589	69.1	30.9	4.3	4.4
1995 Total	5,348,486	2,391,725	7,740,211	69.1	30.9	4.9	4.9
Excluding AIDS	4,820,719	2,155,720	6,976,439	69.1	30.9	n.a.	n.a.
AIDS	527,767	236,005	763,772	69.1	30.9	n.a.	n.a.

Note – – 1992 and prior years data excludes NIMH, NIAAA, and NIDA. Comparable data is not available.

1/ Actual data from the Indirect Cost Management System (ICMS). Includes research project grants, research centers, research career awards, organ systems, clinical education, cooperative clinical research, minority biomedical research support and cancer control grants.

DHHS – NATIONAL INSTITUTES OF HEALTH

FY 1995 Congressional Justification

Full–Time Equivalents

	FY 1993 Actual			FY 1994 Estimate			FY 1995 President's Budget		
INSTITUTE	AIDS	Excludes AIDS	Includes AIDS	AIDS	Excludes AIDS	Includes AIDS	AIDS	Excludes AIDS	Includes AIDS
NCI	300	2,301	2,601	306	2,094	2,400	289	2,042	2,331
NHLBI	34	877	911	42	843	885	36	823	859
NIDR	15	347	362	17	345	362	17	334	351
NIDDK	10	628	638	10	650	660	10	632	642
NINDS	34	675	709	38	678	716	37	659	696
NIAID	369	767	1,136	385	759	1,144	371	740	1,111
NIGMS	2	189	191	2	186	188	2	182	184
NICHD	24	538	562	26	497	523	24	484	508
NEI	9	263	272	9	248	257	8	241	249
NIEHS	7	743	750	8	727	735	8	707	715
NIA	4	468	472	5	453	458	4	441	445
NIAMS	3	163	166	4	146	150	2	148	150
NIDCD	0	133	133	1	116	117	1	116	117
NIMH	45	903	948	46	911	957	43	886	929
NIDA	73	351	424	80	321	401	73	317	390
NIAAA	15	239	254	15	229	244	6	231	237
NINR	6	46	52	10	42	52	7	44	51
NCRR	11	97	108	11	91	102	11	89	100
NCHGR	0	55	55	0	153	153	0	183	183
FIC	4	71	75	4	76	80	4	74	78
Subtotal	965	9,854	10,819	1,019	9,565	10,584	953	9,373	10,326
NLM	10	615	625	10	604	614	10	589	599
OD	41	675	716	42	675	717	38	666	704
Cen. Svcs...	257	4,688	4,945	340	4,549	4,889	340	4,424	4,764
TOTAL, NIH	1,273	15,832	17,105	1,411	15,393	16,804	1,341	15,052	16,393

DHHS – NATIONAL INSTITUTES OF HEALTH
Research Project Grants
Total Number of Awards and Dollars
Includes AIDS
(Dollars in Thousands)

	FY 1985	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990	FY 1991	FY 1992	FY 1993 Bud. Auth.	FY 1994 Estimate	FY 1995 Pres. Bud.
No. of Awards:											
Competing	6,825	6,739	7,197	6,867	6,157	5,620	6,462	6,768	6,177	6,203	7,292
Total (includes Noncomp)	19,710	20,220	21,300	22,017	22,725	22,527	23,352	24,033	24,005	24,010	23,890
Average Annual Cost:											
Competing	$145.2	$148.3	$171.9	$175.2	$182.3	$196.7	$208.1	$220.3	$220.7	$233.9	$240.3
Total (includes Noncomp)	$149.7	$154.4	$175.1	$183.0	$193.9	$205.3	$216.1	$227.2	$237.5	$248.1	$260.0
Percent Change from prior year:											
Competing		2.2%	15.9%	1.9%	4.0%	7.9%	5.8%	5.9%	0.2%	6.0%	2.7%
Total		3.1%	13.4%	4.5%	5.9%	5.9%	5.2%	5.1%	4.5%	4.5%	4.8%
Average Length of Award in Years	3.3	3.6	3.8	4.0	4.1	4.1	3.9	3.9	3.9	3.9	3.9
Average Total Cost (Per competing cycle)	$479.0	$534.0	$653.2	$701.0	$747.5	$806.4	$819.8	$859.0	$860.8	$912.0	$937.0

DHHS -- NATIONAL INSTITUTES OF HEALTH
HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1938 – 1994
(Dollars in Thousands)
(Current Appropriations Only)

FISCAL YEAR	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS
1938	$400	......	......	......	......	......	......	......	......	......	......	......
1939	400	......	......	......	......	......	......	......	......	......	......	......
1940	570	......	......	......	......	......	......	......	......	......	......	......
1941	570	......	......	......	......	......	......	......	......	......	......	......
1942	565	......	......	......	......	......	......	......	......	......	......	......
1943	535	......	......	......	......	......	......	......	......	......	......	......
1944	530	......	......	......	......	......	......	......	......	......	......	......
1945	561	......	......	......	......	......	......	......	......	......	......	......
1946	549	......	......	......	......	......	......	......	......	......	......	......
1947	1,821	......	......	......	......	......	......	......	......	......	......	......
1948	14,500	......	......	......	......	......	......	......	......	......	......	......
1949	14,000	......	......	......	......	......	......	......	......	......	......	......
1950	18,900	$10,725	$1,780	......	......	......	......	......	......	......	......	......
1951	20,086	14,200	1,955	......	......	......	......	......	......	......	......	......
1952	19,657	10,083	1,618	......	......	......	......	......	......	......	......	......
1953	17,887	12,000	1,650	......	......	......	......	......	......	......	......	......
1954	20,237	15,168	1,740	$7,000	$4,500	$5,738	......	......	......	......	......	......
1955	21,737	16,668	1,990	8,270	7,601	6,180	......	......	......	......	......	......
1956	24,978	18,898	2,176	10,840	9,861	7,775	......	......	......	......	......	......
1957	48,432	33,396	6,026	15,885	18,650	13,299	......	......	......	......	......	......
1958	56,402	35,936	6,430	20,385	21,387	17,400	......	......	......	......	......	......
1959	75,268	45,613	7,420	31,215	29,403	24,071	......	......	......	......	......	......
1960	91,257	62,237	10,019	46,862	41,487	34,054	......	......	......	......	......	......
1961	111,000	86,900	15,500	61,200	56,600	44,000	......	......	......	......	......	......
1962	142,836	132,912	17,340	81,831	70,812	56,091	......	......	......	......	......	......
1963	155,742	147,398	21,199	103,388	83,506	66,142	......	......	......	......	......	......
1964	144,340	132,404	19,689	113,679	87,675	68,723	......	(34,000)1/	......	......	......	......
1965	150,011	124,824	20,083	113,050	87,821	69,847	......	42,696	......	......	......	......
1966	163,768	141,462	23,677	123,203	101,153	77,987	$127,188	55,024	......	......	......	......
1967	175,656	164,770	28,308	135,687	116,296	90,670	145,113	64,922	......	$24,298	......	......
1968	183,356	167,954	30,307	143,954	128,633	94,422	160,284	68,621	......	17,289	......	......
1969	185,150	166,928	29,984	143,888	128,935	96,841	163,514	73,127	......	17,820	......	......

FISCAL YEAR	NIDCD	NIMH	NIDA	NIAAA	NCRR	NINR	NCHGR	FIC	NLM	OD	B&F	TOTAL
1938	......	......	......	......	$64	......	......	......	......	......	......	$464
1939	......	......	......	......	64	......	......	......	......	......	......	464
1940	......	......	......	......	137	......	......	......	......	......	......	707
1941	......	......	......	......	141	......	......	......	......	......	......	711
1942	......	......	......	......	135	......	......	......	......	......	......	700
1943	......	......	......	......	743	......	......	......	......	......	......	1,278
1944	......	......	......	......	2,025	......	......	......	......	......	......	2,555
1945	......	......	......	......	2,274	......	......	......	......	......	......	2,835
1946	......	......	......	......	2,866	......	......	......	......	......	......	3,415
1947	......	......	......	......	6,254	......	......	......	......	......	......	8,075
1948	......	......	......	......	10,126	......	......	......	......	......	......	24,626
1949	......	......	......	......	14,540	......	......	......	......	......	......	28,540
1950	......	......	......	......	12,075	......	......	......	......	......	......	43,480
1951	......	......	......	......	14,314	......	......	......	......	......	......	50,555
1952	......	......	......	......	15,757	......	......	......	......	......	......	47,115
1953	......	......	......	......	16,599	......	......	......	......	......	......	48,136
1954	......	......	......	......	4,675	......	......	......	......	......	......	59,058
1955	......	......	......	......	4,675	......	......	......	......	......	......	67,121
1956	......	......	......	......	5,929	......	......	......	......	......	......	80,457
1957	......	......	......	......	12,122	......	......	......	......	......	......	147,810
1958	......	......	......	......	14,026	......	......	......	......	......	......	171,966
1959	......	......	......	......	28,974	......	......	......	......	......	......	241,964
1960	......	......	......	......	45,994	......	......	......	......	......	......	331,910
1961	......	......	......	......	83,900	......	......	......	......	......	......	459,100
1962	......	......	......	......	127,637	......	......	......	......	......	......	629,459
1963	......	......	......	......	159,826	......	......	......	......	......	......	737,201
1964	......	......	......	......	163,869	......	......	......	......	......	......	730,379
1965	......	......	......	......	164,759	......	......	......	......	......	......	773,091
1966	......	......	......	......	60,469 2/	......	......	......	......	......	......	873,931
1967	......	......	......	......	68,534	......	......	......	......	......	......	1,014,254
1968	......	......	......	......	81,141	......	......	$500	......	......	......	1,076,461
1969	......	......	......	......	84,810	......	......	600	$18,160	......	......	1,109,757

DHHS -- NATIONAL INSTITUTES OF HEALTH
HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1938 – 1994
(Dollars in Thousands)
(Current Appropriations Only)

FISCAL YEAR	NCI	NHLBI	NIDR	NIDDK	NINDS	NIAID	NIGMS	NICHD	NEI	NIEHS	NIA	NIAMS
1970	181,454	160,634	26,754	131,761	97,315 3/	97,342	148,294	76,095	$22,826	17,423	......	......
1971	233,160	194,925	35,440	137,986	103,502	102,368	160,194	94,760	30,032	20,151	......	......
1972	378,794	232,627	43,388	153,337	116,732	109,117	173,474	116,427	37,132	26,436	......	......
1973	492,205	300,000	46,991	167,316	130,672	113,414	183,171	130,429	38,562	30,956	......	......
1974	527,486	289,550	43,959	153,561	121,358	111,089	168,329	125,455	41,177	28,397	......	......
1975	691,666	324,630	50,033	173,514	142,498	119,452	187,400	142,435	44,133	35,171	......	......
1976	761,727	370,013	51,291	179,516	144,446	126,852	187,312	136,404	50,212	37,660	$19,288	......
1976 T.Q.	152,901	58,763	7,854	43,719	34,272	27,638	34,078	24,201	4,038	9,519	8,743	......
1977	815,000	396,661	55,573	219,600	155,500	141,000	205,000	145,543	64,000	51,141	30,000	......
1978	872,388	447,909	61,728	260,253	178,438	162,341	230,796	166,390	85,400	64,241	37,305	......
1979	937,129	510,526	65,213	302,767	212,365	191,328	277,628	197,630	105,192	76,080	56,911	......
1980	999,869	527,488	68,303	341,206	241,966	215,364	312,468	208,953	112,989	83,893	69,988	......
1981	989,355	549,693	71,114	369,462	252,533	232,077	333,764	220,628	117,983	93,491	75,606	......
1982	986,617	559,637	71,863	368,191	265,901	235,895	339,862	226,309	127,374	106,270	81,903	......
1983	987,642	624,259	79,292	413,492	297,064	279,129	369,813	254,324	141,901	164,867	93,986	......
1984	1,081,581	704,939	88,674	464,026	335,883	319,596	415,937	276,046	155,131	180,597	115,292	......
1985	1,183,806	805,269	100,688	543,576	396,865	370,965	482,260	313,295	181,678	194,819	144,521	......
1986	1,203,369	822,292	98,841	544,858	414,727	368,964	492,630	307,958	186,705	188,986	149,762	......
1987	1,402,837	930,001	117,945	511,124	490,233	545,523	570,916	366,780	216,637	209,294	177,681	$136,713
1988	1,469,327	965,536	126,297	534,733	534,692	638,800	632,676	396,811	224,947	215,666	194,746	147,679
1989	1,570,349	1,045,509	130,709	559,494	472,291	740,257	682,213	425,375	231,170	223,403	222,639	159,891
1990	1,634,332	1,072,354	135,749	581,477	490,409	832,977	681,782	442,914	236,533	229,234	239,455	166,930
1991	1,714,784	1,126,942	148,918	615,272	541,743	906,251	760,010	478,956	253,241	241,028	323,752	193,247
1992	1,962,587	1,188,593	158,417	658,925	577,938	959,082	816,844	518,251	268,978	248,575	383,382	203,047
1993	1,981,351	1,214,793	161,301	681,342	600,076	979,471	832,581	527,788	276,168	251,167	399,924	212,456
1994	2,082,267	1,277,880	169,520	716,054	630,650	1,065,583	875,511	555,195	290,260	264,249	420,303	223,280

NOTE: Includes $10,000, transferred from "Special Cancer Research" appropriation.

1/ Congress authorized the transfer of $34,000 from other NIH appropriations to establish the "National Institute of Child Health and Human Develo

2/ Excludes the "National Institute of General Medical Sciences" established as a separate appropriation.

3/ Excludes funds for blindness, established as a separate appropriation "National Eye Institute".

4/ Excludes the "Office of International Operations", transferred to the "National Institute of Allergy and Infectious Diseases" and "John E. Fogarty International Center for Advanced Study in the Health Sciences".

5/ Prior to 1970, previously funded under NIH Management Fund.

6/ Prior to 1970, previously funded under DHEW health activities.

7/ Reflects a 1.2% administrative reduction and procurement reform and transfer to OASH for AZT.

8/ Reflects reductions for Extramural Salary Cap, Procurement Reform, S&E, and Sequestration.

9/ Reflects 2.41% reduction and NIH's share of the $50M reduction for Salaries and Expenses.

10/ Reflects reductions for travel and Salaries and Expenses.

11/ Reflects an across the board .8 percent reduction and reductions for Salaries and Expenses and Consultant Services. Reflects real transfer of $

12/ National Center of Nursing Research elevated to Institute status in 1994.

FISCAL YEAR	NIDCD	NIMH	NIDA	NIAAA	NCRR	NINR	NCHGR	FIC	NLM	OD	B&F	TOTAL
1970	......	......	......	......	67,925 4/	......	......	2,775	19,251	$7,541 5/	$1,615 6/	1,061,007
1971	......	......	......	......	66,320	......	......	3,666	21,440	8,903	......	1,212,847
1972	......	......	......	......	74,981	......	......	4,307	24,127	11,712	3,565	1,506,156
1973	......	......	......	......	75,073	......	......	4,666	28,568	12,042	8,500	1,762,565
1974	......	......	......	......	129,426	......	......	4,767	25,871	12,000	8,000	1,790,425
1975	......	......	......	......	127,200	......	......	5,589	28,850	17,326	3,000	2,092,897
1976	......	......	......	......	130,265	......	......	5,705	29,065	18,370	54,000	2,302,126
1976 T.Q.	......	......	......	......	20,282	......	......	1,135	6,572	4,642	750	439,107
1977	......	......	......	......	137,500	......	......	7,992	35,234	16,934	67,400	2,544,078
1978	......	......	......	......	145,095	......	......	8,483	37,619	18,900	65,650	2,842,936
1979	......	......	......	......	154,164	......	......	8,989	41,431	19,673	30,950	3,189,976
1980	......	......	......	......	169,196	......	......	8,987	43,979	21,036	3,250	3,428,935
1981	......	......	......	......	175,627	......	......	9,124	44,666	22,531	11,750	3,569,406
1982	......	......	......	......	184,177	......	......	9,205	45,035	23,618	9,898	3,641,875
1983	......	......	......	......	213,917	......	......	10,147	51,943	24,683	17,500	4,023,969
1984	......	......	......	......	243,177	......	......	11,336	49,613	26,720	25,040	4,493,588
1985	......	......	......	......	304,025	......	......	11,728	55,910	38,304	21,730	5,149,459
1986	......	......	......	......	292,523	......	......	11,054	55,322	111,961	14,259	5,262,211
1987	......	......	......	......	322,860	$20,000	......	11,420	61,838	57,208	31,900	6,182,910
1988	......	......	......	......	368,153	23,380	......	15,651	67,910	61,819	47,870	6,666,693
1989	$94,166	......	......	......	358,076	29,133	......	15,790	73,731	72,076	38,492	7,144,764 7/
1990	117,583	......	......	......	353,734	33,513	$59,538	15,516	81,861	107,419	61,042	7,576,352 8/
1991	134,935	......	......	......	335,255	39,722	87,418	17,519	91,408	97,651	168,687	8,276,739 9/
1992	148,789	......	......	......	314,213	44,929	104,762	19,593	99,088	141,854	103,840	8,921,687 10/
1993	154,814	$583,651	$403,806	$176,619	312,468	48,119	106,239	19,733	113,031	190,325	108,731	10,335,996 11/
1994	162,823	613,444	425,201	185,617	331,915	51,018	128,701	21,677	119,981	233,605	111,039	10,955,773 12/

NATIONAL INSTITUTES OF HEALTH

1995 CONGRESSIONAL JUSTIFICATION
NIH Total

Budget Authority by Object

	FY 1994 Estimate	FY 1995 Pres. Bud.	Increase/Decrease
Personnel Compensation:			
Full−time Permanent	445,638,000	450,999,000	+$5,361,000
Other than full−time permanent	119,500,000	119,144,000	−356,000
Other personnel compensation	22,473,000	23,227,000	+754,000
Special personal services payments	57,330,000	61,615,000	+4,285,000
Total, Personnel Compensation	644,941,000	654,985,000	+10,044,000
Personnel Benefits			
Civilian personnel benefits	134,295,000	135,400,000	+1,105,000
Benefits or former personnel	411,000	411,000	−−−
Travel and transportation of persons	20,293,000	21,044,000	+751,000
Transportation of things	3,962,000	4,113,000	+151,000
Rental payment to GSA	3,440,000	3,612,000	+172,000
Rental payments to others	7,632,000	7,732,000	+100,000
Communications, utilities, and miscellaneous charges	40,720,000	41,733,000	+1,013,000
Printing and reproduction	16,587,000	16,960,000	+373,000
Consulting services	30,897,000	31,983,000	+1,086,000
Other Services	358,395,000	365,604,000	+7,209,000
Purchases from Govt. Accts.	702,336,000	749,111,000	+46,775,000
Operation of GOCOs	71,482,000	71,518,000	+36,000
R&D Contracts	787,788,000	845,894,000	+58,106,000
Supplies and materials	117,835,000	124,042,000	+6,207,000
Equipment	89,557,000	91,044,000	+1,487,000
Grants, subsidies, and contributions	7,925,201,000	8,307,814,000	+382,613,000
Interest and dividends	1,000	−−−	−1,000
Total Obligations	10,955,773,000	11,473,000,000	+517,227,000

NATIONAL INSTITUTES OF HEALTH

1995 CONGRESSIONAL JUSTIFICATION
Non-AIDS

Budget Authority by Object

	FY 1994 Estimate	FY 1995 Estimate	Increase or Decrease
Personnel Compensation:			
Full-time Permanent	405,821,000	410,532,000	+$4,711,000
Other than full-time permanent	107,786,000	107,300,000	-486,000
Other personnel compensation	20,387,000	21,138,000	+751,000
Special personal services payments	52,778,000	57,049,000	+4,271,000
Total, Personnel Compensation	586,772,000	596,019,000	+9,247,000
Personnel Benefits			
Civilian personnel benefits	121,371,000	122,117,000	+746,000
Benefits or former personnel	411,000	411,000	---
Travel and transportation of persons	17,657,000	18,197,000	+540,000
Transportation of things	3,531,000	3,681,000	+150,000
Rental payment to GSA	1,868,000	1,969,000	+101,000
Rental payments to others	6,963,000	6,975,000	+12,000
Communications, utilities, and miscellaneous charges	37,452,000	38,080,000	+628,000
Printing and reproduction	15,413,000	15,848,000	+435,000
Consulting services	25,596,000	26,634,000	+1,038,000
Other Services	269,671,000	274,640,000	+4,969,000
Purchases from Govt. Accts.	630,848,000	675,460,000	+44,612,000
Operation of GOCOs	64,735,000	64,766,000	+31,000
R&D Contracts	524,814,000	568,940,000	+44,126,000
Supplies and materials	93,578,000	99,089,000	+5,511,000
Equipment	79,582,000	81,311,000	+1,729,000
Grants, subsidies, and contributions	7,174,465,000	7,499,811,000	+325,346,000
Interest and dividends	1,000	---	-1,000
Total Obligations	9,654,728,000	10,093,948,000	+439,220,000

NATIONAL INSTITUTES OF HEALTH

1995 CONGRESSIONAL JUSTIFICATION
AIDS

Budget Authority by Object

	FY 1994 Estimate	FY 1995 Estimate	Increase or Decrease
Personnel Compensation:			
Full–time Permanent	39,817,000	40,467,000	+$650,000
Other than full–time permanent	11,714,000	11,844,000	+130,000
Other personnel compensation	2,086,000	2,089,000	+3,000
Special personal services payments	4,552,000	4,566,000	+14,000
Total, Personnel Compensation	58,169,000	58,966,000	+797,000
Personnel Benefits			
Civilian personnel benefits	12,924,000	13,283,000	+359,000
Benefits or former personnel			
Travel and transportation of persons	2,636,000	2,847,000	+211,000
Transportation of things	431,000	432,000	+1,000
Rental payment to GSA	1,572,000	1,643,000	+71,000
Rental payments to others	669,000	757,000	+88,000
Communications, utilities, and miscellaneous charges	3,268,000	3,653,000	+385,000
Printing and reproduction	1,174,000	1,112,000	−62,000
Consulting services	5,301,000	5,349,000	+48,000
Other Services	88,724,000	90,964,000	+2,240,000
Purchases from Govt. Accts.	71,488,000	73,651,000	+2,163,000
Operation of GOCOs	6,747,000	6,752,000	+5,000
R&D Contracts	262,974,000	276,954,000	+13,980,000
Supplies and materials	24,257,000	24,953,000	+696,000
Equipment	9,975,000	9,733,000	−242,000
Grants, subsidies, and contributions	750,736,000	808,003,000	+57,267,000
Total Obligations	1,301,045,000	1,379,052,000	+78,007,000

NATIONAL INSTITUTES OF HEALTH

1995 CONGRESSIONAL JUSTIFICATION

Budget Authority by Object
including
Service and Supply Fund
Management Fund

	FY 1994 Estimate	FY 1995 Pres. Bud.	Increase/Decrease
Personnel Compensation:			
Full–time Permanent	$605,727,000	$616,163,000	+$10,436,000
Other than full–time permanent	132,676,000	132,669,000	−7,000
Other personnel compensation	37,903,000	38,867,000	+964,000
Special personal services payments	58,332,000	62,656,000	+4,324,000
Total, Personnel Compensation	834,638,000	850,355,000	+15,717,000
Personnel Benefits			
Civilian personnel benefits	169,709,000	171,736,000	+2,027,000
Benefits or former personnel	696,000	637,000	−59,000
Travel and transportation of persons	19,283,000	20,067,000	+784,000
Transportation of things	5,278,000	5,513,000	+235,000
Rental payment to GSA	3,440,000	3,612,000	+172,000
Rental payments to others	7,632,000	7,732,000	+100,000
Communications, utilities, and miscellaneous charges	62,004,000	64,732,000	+2,728,000
Printing and reproduction	17,869,000	18,776,000	+907,000
Consulting services	30,897,000	31,983,000	+1,086,000
Other Services	513,690,000	520,775,000	+7,085,000
Purchases from Govt. Accts.	235,389,000	271,424,000	+36,035,000
Operation of GOCOs	71,482,000	71,518,000	+36,000
R&D Contracts	787,788,000	845,894,000	+58,106,000
Supplies and materials	155,863,000	167,065,000	+11,202,000
Equipment	114,913,000	113,367,000	−1,546,000
Grants, subsidies, and contributions	7,925,201,000	8,307,814,000	+382,613,000
Interest and dividends	1,000	---	−1,000
Total Obligations	10,955,773,000	11,473,000,000	+517,227,000

NATIONAL INSTITUTES OF HEALTH

Justification

Management Fund

General Statement

The NIH Management Fund (MF) was established on June 29, 1957, by Public Law 85-67. The MF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The expenses for these activities are paid by the NIH appropriations and other government agencies. The services provided by the MF include utilities and plant maintenance, a 500 bed hospital and outpatient clinic, receipt, review and referral of research and training grant applications, collaborative computer science research and biomedical engineering, and general administrative support services.

NATIONAL INSTITUTES OF HEALTH

Management Fund

Source of Income

	1993 Actual	1994 Estimate	1995 Estimate
NCI.............	134,736,000	137,831,000	141,317,000
NHLBI...........	45,897,000	48,777,000	50,032,000
NIDR...........	8,544,000	9,396,000	9,596,000
NIDDK	27,331,000	28,826,000	29,435,000
NINDS...........	31,612,000	34,934,000	33,811,000
NIAID...........	38,322,000	33,813,000	34,277,000
NIGMS...........	7,725,000	7,935,000	8,376,000
NICHD...........	27,027,000	26,954,000	27,832,000
NEI.............	9,493,000	10,279,000	10,488,000
NIEHS...........	2,749,000	2,451,000	2,533,000
NIA.............	7,735,000	7,020,000	7,123,000
NIAMS...........	7,710,000	8,297,000	8,525,000
NIDCD...........	2,270,000	2,684,000	2,783,000
NIMH............	32,699,000	32,711,000	33,329,000
NIDA............	393,000	472,000	499,000
NIAAA...........	5,777,000	6,834,000	6,901,000
NCRR............	3,387,000	3,871,000	4,088,000
NCNR............	972,000	1,076,000	1,115,000
NCHGR...........	774,000	2,016,000	2,066,000
FIC.............	1,103,000	1,192,000	1,195,000
NLM.............	9,838,000	9,360,000	9,486,000
FDA.............	7,014,000	7,363,000	7,412,000
SSF.............	9,843,000	10,426,000	11,023,000
SUBTOTAL	422,951,000	434,518,000	443,242,000
INTRAFUND BILLING.......	23,942,000	24,918,000	25,558,000
DIRECT REIMBURSEMENTS	2,684,000	4,895,000	6,211,000
	449,577,000	464,331,000	475,011,000

NATIONAL INSTITUTES OF HEALTH

Management Fund

Obligations By Activity
(Dollars in thousands)

	1993 Actual FTEs	Amount	1994 Estimate FTEs	Amount	1995 Estimate FTEs	Amount
Computer Services..........	127	20,195	118	20,496	115	21,190
Intramural scientific services.................	220	25,687	230	25,952	225	26,264
Clinical services..........	2,144	218,483	2,114	221,743	2,060	227,612
Grant review and approval.................	437	35,735	430	36,574	419	38,241
Intramural research support services.........	828	125,578	796	136,457	775	134,945
Rental payments............	---	23,899	---	23,109	---	26,759
Total Obligations..........	3,756	449,577	3,688	464,331	3,594	475,011

NATIONAL INSTITUTES OF HEALTH

Management Fund

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	3,688	3,594	-94
Full-time equivalent of overtime and holiday hours	168	166	-2
Average ES salary	$109,222	$111,444	+$2,222
Average GM/GS grade	12.80	12.80	
Average GM/GS salary	51,278	52,914	+1,636
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	59,815	62,158	+2,343
Average salary of ungraded positions	32,363	33,062	+699
Full-time permanent	140,562,000	144,588,000	+4,026,000
Other than full-time permanent	11,645,000	11,913,000	+268,000
Other personnel compensation	11,476,000	11,644,000	+168,000
Special personnel services	1,002,000	1,041,000	+39,000
Subtotal Personnel Compensation	164,685,000	169,186,000	+4,501,000
Personnel benefits	36,663,000	37,539,000	+876,000
Benefits for former personnel	258,000	199,000	-59,000
Travel and transportation of persons ..	1,208,000	1,276,000	+68,000
Transportation of things	872,000	961,000	+89,000
Rent, communications and utilities	59,823,000	62,611,000	+2,788,000
Printing and reproduction	2,479,000	2,331,000	-148,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Other services	134,136,000	132,673,000	-1,463,000
Supplies and materials	44,687,000	48,943,000	+4,256,000
Equipment	19,520,000	19,292,000	-228,000
TOTAL	464,331,000	475,011,000	+10,680,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

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NATIONAL INSTITUTES OF HEALTH

Justification

Service and Supply Fund

General Statement

The NIH Service and Supply Fund (SSF) was established on April 11, 1953, under 42 U.S.C. 231. The SSF was created to finance a variety of centralized research support services and administrative activities which are required for the efficient and effective operation of all NIH programs and facilities. The SSF provides a single means for consolidating the financing and accounting of business-type operations involving the sales of services and commodities to customers. The services provided by the SSF include mainframe computing, engineering planning and design, printing, telecommunications, procurement, shipping and receiving, motor pool, research animals, fabrication and maintenance of scientific equipment, and other administrative support services.

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Obligations By Activity
(dollars in thousands)

	1993 Actual		1994 Estimate		1995 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Administrative Services:						
Cost of Goods Sold.......		$39,776		$40,154		$42,030
Other....................	828	124,853	845	141,418	823	145,632
Data processing services...	198	31,681	185	45,000	180	47,153
Instrumentation:						
Cost of Goods Sold.......		3,619		3,619		3,619
Other....................	74	9,539	70	9,047	68	9,339
Research animals...........	89	16,482	102	22,347	100	19,828
Total Obligations..........	1,189	225,950	1,202	261,585	1,171	267,601

NATIONAL INSTITUTES OF HEALTH

Service and Supply Fund

Budget Authority by Object

	1994 Current Estimate	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	1,202	1,171	-31
Full-time equivalent of overtime and holiday hours	59	62	+3
Average ES salary	$112,000	$114,000	+$2,000
Average GM/GS grade	10.9	10.10	.1
Average GM/GS salary	39,538	40,944	+1,406
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	56,385	57,231	+846
Average salary of ungraded positions	32,709	33,314	+605
Personnel compensation:			
Full-time permanent	$45,424,000	$46,999,000	+$1,575,000
Other than full-time permanent	1,531,000	1,612,000	+81,000
Other personnel compensation	3,954,000	3,996,000	+42,000
Special personnel services	---	---	---
Subtotal Personnel Compensation	50,909,000	52,607,000	+1,698,000
Personnel benefits	9,110,000	9,393,000	+283,000
Benefits for former personnel	27,000	27,000	---
Travel and Transportation of persons ...	372,000	396,000	+24,000

	1994 Current Estimate	1995 Estimate	Increase or Decrease
Transportation of things	444,000	439,000	-5,000
Rent, communications and utilities	39,152,000	39,935,000	+783,000
Printing and reproduction	3,982,000	4,784,000	+802,000
Other services	93,670,000	96,677,000	+3,007,000
Supplies and materials	50,314,000	52,364,000	+2,050,000
Equipment	13,605,000	10,979,000	-2,626,000
TOTAL	261,585,000	267,601,000	+6,016,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

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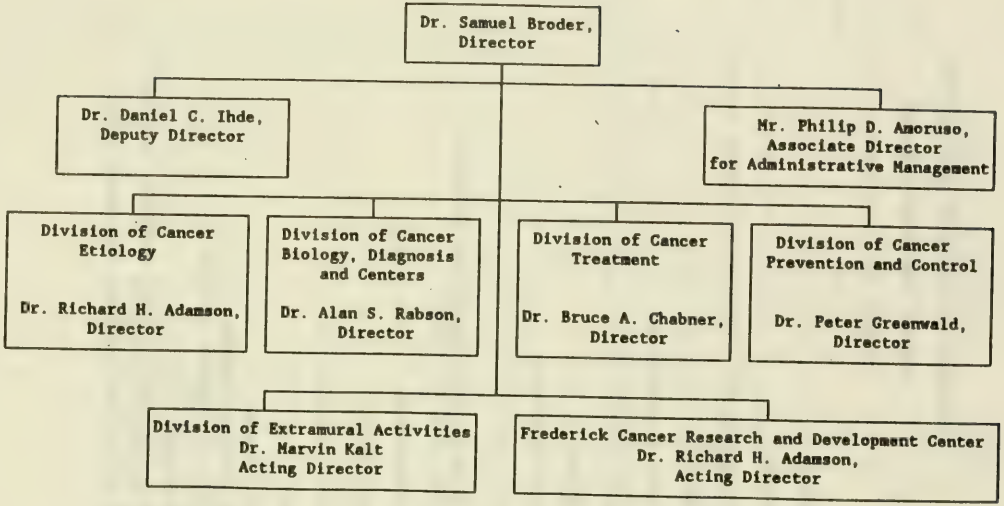
NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cancer [$2,082,267,000] $1,967,709,000, *of which $22,938,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriation Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Language Analysis

Language Provision	Explanation
"...of which $22,938,000 shall not become available for obligation until September 19, 1995."	This language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation [1]

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation....................	$2,007,483,000	$2,082,267,000	$1,967,709,000
Section 511 .8% reduction.........	-16,060,000	---	---
Section 513 Cons. Srvcs reduction.	-139,000	---	---
Section 216 S&E reduction.........	-9,933,000	---	---
Subtotal adjusted appropriation	1,981,351,000	2,082,267,000	1,967,709,000
Real transfer to other NIH accounts for Tuberculosis Research.......	-1,931,000	---	---
Real transfer to Food and Drug Administration for Mammography Quality Standards Act...........	-1,000,000	---	---
Comparative transfer to the Office of AIDS Research, NIH for HIV activities..............	-173,029,000	-213,457,000	---
Subtotal adjusted budget authority	1,805,391,000	1,868,810,000	1,967,709,000
Unobligated balance lapsing.......	-80,000	---	---
Total obligations.................	1,805,311,000	1,868,810,000	1,967,709,000

[1] Excludes the following amounts for reimbursable activities carried out under this account: 1993 -- $14,077,000 and 1 FTE; 1994 -- $20,000,000 and 1 FTE; 1995 -- $25,000,000 and 1 FTE.

Note: Excludes $2,686,000 for royalties received in FY 1993 and $5,940,000 in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
Research grants	No.	Amount	No.	Amount	No.	Amount
Research projects:						
Noncompeting..................	2286	$659,639,000	2383	$694,945,000	2181	$666,571,000
Administrative supplementals...	(215)	14,971,000	(171)	12,000,000	(171)	12,480,000
Competing:						
Renewal......................	321	103,726,000	280	90,771,520	389	126,238,000
New..........................	624	109,653,000	563	107,268,480	662	130,863,000
Supplemental.................	7	1,698,000	4	1,354,000	1	38,000
Subtotal, competing............	952	215,077,000	847	199,394,000	1052	257,139,000
Subtotal, research projects...	3238	889,687,000	3230	906,339,000	3233	936,190,000
Research centers:						
Basic research................	14	21,265,000	12	23,487,000	12	23,444,000
Clinical/comprehensive.........	43	98,900,000	42	100,344,000	44	106,961,000
Subtotal, Core Grants.........	57	120,165,000	54	123,831,000	56	130,405,000
SPORE Grants..................	22	21,465,000	23	26,816,000	26	31,232,000
Subtotal, Centers and SPOREs..	79	141,630,000	77	150,647,000	82	161,637,000
Other research:						
Research career program........	161	14,045,000	171	14,386,000	171	15,201,000
Cancer education..............	78	7,815,000	73	7,904,000	80	8,904,000
Cooperative clinical research..	158	73,251,000	232	77,233,000	233	78,955,000
Minority biomedical research support.............		2,959,000		3,099,000		3,223,000
Other research related.........	146	7,957,000	287	13,031,000	312	14,491,000
Subtotal, other research......	543	106,027,000	763	115,653,000	796	120,774,000
Total, research grants...........	3860	1,137,344,000	4070	1,172,639,000	4111	1,218,601,000

Training:						
Individual awards:						
Noncompeting	97	2,402,000	98	2,713,000	99	2,946,000
Competing	78	1,951,000	65	1,610,000	64	1,498,000
Subtotal, individual	175	4,353,000	163	4,323,000	163	4,444,000
Institutional awards:						
Noncompeting	1115	28,649,000	1108	29,149,000	724	20,249,000
Competing	156	4,283,000	117	4,019,000	501	13,848,000
Subtotal, institutional	1271	32,932,000	1225	33,168,000	1225	34,097,000
Total, training	1446	37,285,000	1388	37,491,000	1388	38,541,000
Research & development contracts	310	147,550,000	235	124,693,000	245	125,221,000
	FTE		FTE		FTE	
Intramural research	1895	280,764,000	1715	280,974,000	1659	286,183,000
Research management and support	525	89,627,000	516	88,755,000	506	89,525,000
Cancer prevention and control	181	105,293,000	169	145,759,000	166	197,138,000
Construction		7,528,000		18,499,000		12,500,000
Total, NCI	2601	1,805,391,000	2400	1,868,810,000	2331	1,967,709,000
Clinical trials		(279,327,000)		(302,387,000)		(323,548,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

1994 Estimated budget authority	$1,868,810,000
1995 Estimated budget authority	1,967,709,000
Net Change	+98,899,000

	1994 Current Estimate Base		Change from Base	
Changes:	FTE	Budget Authority	FTE	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$112,129,000		+$1,383,000
b. One less day of pay		112,129,000		-430,000
c. Annualization of Jan 1994 locality pay raise		112,129,000		+844,000
d. Jan 1995 pay increases		112,129,000		+1,184,000
e. Federal employees compensation fund, unemployment compensation		112,129,000		+55,000
f. Increased cost of centrally furnished services		106,315,000		+4,370,000
g. Increase for Federal telecommunications system		3,982,500		+16,000
h. Service & supply fund increase		10,076,526		+538,000
i. Increased cost of laboratory materials & other expenses		62,530,000		+2,681,000
Subtotal				+10,641,000
2. Research management & support:				
a. Within grade increase		27,295,000		+336,000
b. One less day of pay		27,295,000		-105,000
c. Annualization of Jan 1994 locality pay raise		27,295,000		+205,000
d. Jan 1995 pay increases		27,295,000		+288,000
e. Federal employees compensation fund, unemployment compensation		27,295,000		+17,000
f. Increased cost of centrally furnished services		11,691,000		+481,000
g. DHHS working capital fund		1,705,296		+10,000
h. Increase for Federal telecommunications system		1,505,000		+6,000
i. Service & supply fund increase		15,121,986		+226,000
j. Increased cost of laboratory materials & other expenses		49,769,000		+1,733,000
Subtotal				+3,197,000

Summary of Changes--continued

	1994 Current Estimate Base		Change from Base	
	No.	Budget Authority	No.	Budget Authority
3. Cancer prevention & control:				
a. Within grade increase.....		$14,511,000		+179,000
b. One less day of pay.......		14,511,000		-56,000
c. Annualization of Jan 1994 locality pay raise..		14,511,000		+109,000
d. Jan 1995 pay increases....		14,511,000		+153,000
e. Federal employees compensation fund, unemployment compensation....		14,511,000		+5,000
f. Increased cost of centrally furnished services.................		1,762,000		+72,000
g. Increase for Federal telecommunications system		500,000		+2,000
h. Service & supply fund increase................		1,086,930		+25,000
i. Increased cost of laboratory materials & other expenses.........		23,137,000		+217,000
Subtotal.......................				+706,000
B. Program:				
1. Research project grants:				
a. Noncompeting.............	2383	706,945,000	-202	-27,894,000
b. Competing................	847	199,394,000	+205	+57,745,000
Subtotal..................	3230	906,339,000	+3	+29,851,000
2. Research centers:				
a. Basic research...........	12	23,487,000	0	-43,000
b. Clinical/comprehensive...	42	100,344,000	+2	+6,617,000
Subtotal..................	54	123,831,000	+2	+6,574,000
c. SPOREs...................	23	26,816,000	+3	+4,416,000
Centers & SPOREs..........	77	150,647,000	+5	+10,990,000
3. Other research...............	763	115,653,000	+33	+5,121,000
Total, research grants.......	4070	1,172,639,000	+41	+45,962,000
4. Research training............	1388	37,491,000	0	+1,050,000
5. R&D contracts................	235	124,693,000	+10	+528,000
	FTE		FTE	
6. Intramural research..........	1715	280,974,000	-56	-5,432,000
7. Research management & support....................	516	88,755,000	-10	-2,427,000
8. Cancer prevention & control.................	169	145,759,000	-3	+50,673,000
9. Construction.................		18,499,000		-5,999,000
Subtotal........................		1,868,810,000		+84,355,000
Total, Changes..................				+98,899,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment....................	2,400	2,331	-69
Full-time equivalent of overtime and holiday hours	24	27	+3
Average ES salary.............	$106,333	$107,396	+$1,063
Average GM/GS grade...........	10.4	10.3	-0.1
Average GM/GS salary..........	$45,214	$45,666	+$452
Average salary, grades established by act of July 1, 1944 [42 USC 207]...	$69,878	$70,576	+$698
Average salary ungraded positions..........	$40,062	$40,462	+$400
Personnel compensation:			
Full-time permanent..........	$83,126,000	$83,422,000	+$296,000
Other than full-time permanent..................	22,299,000	21,626,000	-673,000
Other personnel compensation	4,421,000	4,850,000	+429,000
Special personal services payments...........	15,946,000	17,300,000	+1,354,000
Total personnel compensation	125,792,000	127,198,000	+1,406,000
Personnel benefits............	28,048,000	27,879,000	-169,000
Benefits to former personnel..	95,000	95,000	---

	1994 Appropriation	1995 Estimate	Increase or Decrease
Travel and transportation of persons..................	5,717,000	5,733,000	+16,000
Transportation of things......	1,200,000	1,295,000	+95,000
Rental payments to GSA........	93,000	91,000	-2,000
Rental payments to others.....	3,418,000	3,342,000	-76,000
Communications, utilities, and miscellaneous charges....	10,160,000	10,308,000	+148,000
Printing and reproduction.....	6,094,000	6,377,000	+283,000
Other services:			
Consulting Services..........	8,418,000	8,988,000	+570,000
Other services...............	15,120,000	16,192,000	+1,072,000
Purchases from Govt. Accts...	158,008,000	162,665,000	+4,657,000
Operation of GOCOs...........	63,500,000	63,500,000	---
R&D Contracts................	138,034,000	151,045,000	+13,011,000
Supplies and materials........	24,452,000	24,661,000	+209,000
Equipment.....................	14,236,000	14,606,000	+370,000
Grants, subsidies, and contributions...........	1,266,425,000	1,343,734,000	+77,309,000
Total authority by object....	1,868,810,000	1,967,709,000	+98,899,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

National Institutes of Health
Administrative Costs
Budget Authority
NCI

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	83,126	83,126	83,422	296
11.3	Other than full-time permanent	22,299	22,299	21,626	(673)
11.5	Other personnel compensation	4,421	4,421	4,850	429
11.8	Special personnel services payments	15,946	15,946	17,300	1,354
11.9	Subtotal, personnel compensation	125,792	125,792	127,198	1,406
12.1	Civilian personnel benefits	28,048	28,048	27,879	(169)
13.0	Benefits for former personnel	95	95	95	0
	Subtotal Pay Costs	153,935	153,935	155,172	1,237
21.0	Travel and transportation of persons	5,183	5,717	5,733	16
22.0	Transportation of things	1,195	1,200	1,295	95
23.2	Rental payments to others	3,333	3,418	3,342	(76)
23.3	Communications, utilities, and miscellaneous charges	9,998	10,160	10,308	148
24.0	Printing and reproduction	5,477	6,094	6,377	283
25.0	Other Services	192,715	168,410	174,709	6,299
26.0	Supplies and materials	18,135	24,452	24,661	209
	Subtotal non-pay costs	236,036	219,451	226,425	6,974
	Total Administrative Costs	389,971	373,386	381,597	8,211

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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National Cancer Institute

Significant Items in House, Senate and Conference Appropriations Committee Reports

Item	Action Taken or to be Taken
FY 1994 House Report	
Breast Cancer	
1. "The Committee fully supports the President's commitment to increase NIH funding for breast cancer research. The Committee bill reflects continued support for a multi-year effort to significantly expand research on this critical health problem which kills 46,000 women each year. NCI is expected to expand all facets of breast cancer research, including, basic studies at the genetic level; epidemiology studies focused on environmental carcino-genesis; prevention research and vaccine development; detection research; treatment studies; and rehabilitation efforts." (page 52)	1. NCI will continue to support an integrated approach to breast cancer research. The effects of genetics, environmental\occupational factors (such as pesticides), and hormonal factors on carcinogenesis will be explored. Epidemiology studies on environmental and other factors will be undertaken to investigate the high breast cancer rates found in the northeastern and mid-Atlantic regions of the country. The Long Island Breast Cancer Study Project will assess biological markers of environmental and other potential risk factors for breast cancer in Long Island, NY. Strategies to identify molecular markers and efforts to develop and test preventive regimens will continue. Efforts to develop promising new therapies and vaccines to bolster the antigenic response to tumor cells will be expanded. The accessibility and delivery of state-of-the-art health care to minority women and those who are medically underserved will continue to receive the highest priority, along with community outreach efforts targeted to disadvantaged populations. In FY 1995, NCI will work with the Centers for Disease Control and Prevention to implement the Breast Cancer Action Plan. Objectives include expanded research and training opportunities, linkage of breast cancer databases and other information sources, increased outreach efforts and consumer participation in relevant breast cancer programs.

Item	Action Taken or to be Taken
Prostate Cancer	
2. "The Committee strongly urges the Institute to continue to make prostate cancer research one of its top priorities." (page 52)	2. To help answer important questions about prostate cancer, NCI has planned several large-scale clinical trials in both treatment and screening. The Prostate, Lung, Colon, and Ovary (PLCO) Cancer Screening Trial will compare 37,000 men who will be screened by prostate specific antigen (PSA) levels and rectal examinations to an equal number of men in a control group to determine whether these screening methods reduce mortality rates. A large-scale cooperative trial with the Department of Veterans Affairs medical centers will compare conventional surgery versus observation and palliative management in early stage prostate cancer. The PIVOT study (Prostate Cancer Intervention Versus Observation Trial) will compare mortality, morbidity, quality of life, and other outcome variables in 2,000 men with clinically localized prostate cancer. In addition to clinical trials, basic research on the biology of prostate cancer will stress the identification of factors to predict disease progression. Advances in understanding the role of diet, hormones, growth factors, oncogenes and tumor suppressor genes, and apoptosis (planned cell death) should lead to more effective detection, treatment, and possibly prevention of prostate cancer.
Balance between Basic and Clinical Research	
3. "The Committee recognizes the value of and the need for a balanced cancer research program. Basic research is the foundation for prevention and the development of improved treatments for cancer once it occurs. The Committee believes that basic cancer research must be given equal emphasis with	3. NCI will continue to support basic research efforts which form the basis from which future advances in cancer prevention and treatment will be made. Recognizing the importance of targeting research to address specific disease areas, NCI also places an emphasis on the need for a strong basic research program

Item	Action Taken or to be Taken
disease specific research in allocating scarce research resources." (page 52)	and will allocate resources in order to achieve the optimum balance between these important areas.
Leukemia, Lymphoma and Related Cancers	
4. "The Committee heard testimony about the continuing burden of leukemia, lymphoma and related cancers and supports continued development of research in this area. The Committee urges NCI to consider the full range of research mechanisms as it manages this research." (page 53)	4. NCI will expand its efforts in leukemia, lymphoma and related cancers, and efforts are underway to promote interdisciplinary efforts that target these disease areas. Particular emphasis will be placed on translational research in which basic research advances are quickly incorporated into clinical practice. Ongoing research efforts slated for expansion include bone marrow transplantation studies, gene therapy, stem cell research, investigations into the role of cytokines as hematopoietic growth factors, and studies on the development of secondary leukemias after radiation or chemotherapy to treat a prior malignancy. Other studies will target the impact of environmental and occupational factors on leukemogenesis. A joint workshop with the Leukemia Society was held in January 1994 in order to define the scientific agenda and infrastructure needed to improve the current significant cure rates in many of these disorders.
Bionutrition	
5. "The Committee is supportive of the bionutrition activity of NCI and urges the Institute to utilize a portion of its increase in breast cancer funding to expand the work it is doing regarding the role of nutrition in breast cancer." (page 53)	5. NCI will expand its efforts to study the role of nutrition on breast cancer incidence and recurrence. In particular, the ways in which fat vs. fiber in the diet may influence breast cancer risk will be examined. Other studies will investigate the role of flavonoids in angiogenesis and cellular proliferation, and the effects of heterocyclic amines, ethanol and micronutrients such as retinoids, antioxidants, folate and selenium-trace elements on breast cancer development. Efforts to

Item	Action Taken or to be Taken
	identify biomarkers that can be used to determine the effects of specific dietary components on carcinogenesis or cancer prevention will also be pursued.
Proton Beam Research	
6. "Proton beam research has been supported by NCI because of its potential in the treatment of inoperable cancers and certain vascular diseases. The Committee believes that this research should be continued based on the results to date. The bill includes sufficient resources to finance the next stage of this research initiative." (page 53)	6. NCI has awarded a grant in 1993 to the Massachusetts General Hospital for $7 million for the initial construction phase of a proton beam facility in order to provide geographical access to this promising treatment modality. NCI will continue to support the development of proton beam research.
FY 1994 Senate Report	
Cancer Among American Samoans	
1. "The Committee also encourages the creation of programs aimed at reducing cancer incidence and mortality in native population subgroups. The Committee further urges NCI to continue and expand its efforts to address the incidence of cancer among American Samoans." (page 79)	1. NCI is continuing its commitment to address the special needs of minority populations, including Native Americans. Developmental research is being encouraged through the re-release of a Request For Applications for research studies of Native Pacific populations to assess their cancer prevention, early detection and treatment needs. Additional research studies will assess the needs and identify barriers to cancer prevention and control in communities or organizations within Native Pacific populations. These studies will also test ways in which existing intervention methods can be used or adapted as well as designing new methods that are culturally sensitive to Native Pacific populations. In addition, NCI is developing a network of cancer centers that will address the education, training, and research issues associated with Native American populations, including American Samoans.

Item	Action Taken or to be Taken
Nursing	
2. "The Committee strongly urges the NCI to continue to collaborate with the National Institute of Nursing Research [NINR] on symptom management and prevention of breast cancer and prostate cancer." (page 79)	2. NCI is cofunding several initiatives with the National Institute for Nursing Research (NINR) that include studies in the quality of life assessment in special populations and interventions to enhance adjustment to cancer risk or diagnosis. Cooperative efforts to be pursued between NCI and NINR include studies of pain management, the quality of life of adult cancer survivors, and community models of care that focus on rural and inner city communities. Additional collaborative studies between NCI and NINR will include studies involving symptom management and the prevention of breast and prostate cancer.
Cancer Centers	
3. "The Committee encourages NCI to use all available mechanisms to fully fund cancer center core grants at peer-reviewed levels. The Committee also continues to support expanding the cancer centers network to geographically underrepresented areas of the country and other underserved populations. The Committee looks forward to the current cancer center planning grants recipients, including the University of Iowa, becoming fully designated cancer centers." (page 79)	3. A total of 54 Cancer Centers will be funded in FY 1994, the majority of which will be fully funded at peer-reviewed levels. NCI will work to achieve a balance in the centers program and to extend the geographic distribution of centers to underrepresented areas to meet the needs of underserved populations.
4. "The Committee believes NCI-supported cancer centers should establish the standard of treatment for cancer. Noting the increasing evidence that providing psychotherapeutic support services for cancer patients and their families is a low-cost, highly effective addition to other medical treatment, the Committee believes NCI should require cancer centers to provide supportive psychotherapeutic	4. NCI recognizes the importance of providing psychosocial services to cancer patients currently being treated in cancer centers. While core support to cancer centers does not provide support for patient care services per se, NCI-designated comprehensive cancer centers must address quality of life issues and develop training and education programs in psychosocial services which include an emphasis on hospice

Item	Action Taken or to be Taken
services to cancer patients at all stages of diagnosis and treatment, and to their families. Such services should include, but not be limited to, individual counseling and education, group therapy for patients, and individual and group support for families. Centers should also include in routine care for patients screening and treatment for concurrent psychiatric disorders such as depression and anxiety." (page 79)	programs. Centers are encouraged to work with NCI's Office of Cancer Communications to develop and implement a program of comprehensive psychosocial services. These services include counseling and education, group therapy and support for both patients and their families.
Cancer Prevention and Control	
5. "The Committee commends NCI for starting to develop research programs in psychosocial intervention and strongly urges NCI to continue and expand this research throughout the Institute. In particular, the Committee directs the Division of Cancer Prevention and Control [DCPC] to increase funding for clinical intervention trails that reflect the concerns of cancer patients, survivors, and their families in coping with cancer, such as outpatient pain management; professionally led support and self-help groups; increasing treatment adherence; managing side effects such as nausea; and identifying and reducing other barriers to treatment such as financial, cultural, and geographic obstacles. The Committee commends DCPC for its cooperative research program with the National Institute of Mental Health on the psychosocial and social factors such as stress and support on physiological variables such as endocrine and immune function, and disease progression." (page 80)	5. The NCI places a high priority on psycho-social research, particularly as it relates to the concerns of cancer patients, cancer survivors and their families in coping with the unique burdens associated with cancer. A new Request for Applications (RFA) on the management of cancer pain outside of the acute care or hospice setting seeks to improve the quality of life of persons with cancer who are living at home or who are being managed on an out-patient basis. Research on interventions to facilitate the reintegration of adult cancer survivors into their pre-illness society and environment is also being pursued. In October 1993, NCI held a planning meeting on future directions in cancer prevention and control behavioral and psychosocial research and will participate in an upcoming trans-NIH conference on the psychoneuroimmunological aspects of health and disease. Cooperative efforts between the NCI and National Institute of Mental Health include research plan development and shared efforts in providing funding for applications dealing with aspects of psychosocial research of relevance to both Institutes.

Item	Action Taken or to be Taken
Cancer Prevention and Control	
6. "The Committee is concerned about the many adolescents, particularly minority and low-income teenagers, who are at high risk of cancer due to their use of tobacco, alcohol and drugs and their involvement in high-risk sexual activity. The Committee urges the Institute to support research on educational interventions intended to reach this population. The Committee also encourages the Institute to expand the study of new screening and intervention strategies for familial cancers, such as neurofibromatosis." (page 80)	6. NCI re-released a Program Announcement for research on cancer risk reduction for high risk youth in January 1994. The research objectives include the development and testing through community institutions, methods and interventions for the primary prevention of cancers related to poor diet, tobacco use, alcohol use, and early sexual activity in adolescents from low-socioeconomic groups. NCI investigators collaborated in pioneering studies to map and isolate the gene for neurofibromatosis 2 (NF2), which resulted in the isolation and sequencing of this gene and identification of its protein product in March 1993. NCI will continue to pursue studies at the molecular level, along with efforts to screen for the NF2 gene in a large number of NF2 patients to identify family-specific mutations that may be correlated with clinical manifestations. Such information will be useful in counseling patients about long-term prognosis and management options. Therapeutic strategies developed from knowledge of the NF2 gene may have wider application for the treatment of other genetic diseases.
Diethylstilbestrol	
7. "The Committee continues to strongly support increased efforts to support the study of and public education regarding exposure to the synthetic hormone diethylstilbestrol (DES). NCI and other Institutes, along with the Office of Women's Health have developed a plan for expanded activities in these areas. The Committee has included sufficient funds for NCI to significantly expand on its fiscal year 1993 levels of support for both its research and education efforts	7. NCI continues to support a broad range of DES studies and will expand ongoing research and educational efforts in this area. A large, multicenter cohort study of exposed mothers and their offspring is being carried out to determine increased incidence of cancer, autoimmune disease, and reproductive problems. NCI issued an RFA for continued follow-up and study of clear cell adenocarcinoma patients and DES exposure. These studies will assess the determinants of survival,

Item	Action Taken or to be Taken
in this area. These funds should be directed at implementing the provisions of the DES Education and Research Amendments of 1992 and the recommendations of the action plan developed last year." (page 80)	recurrence and other health outcomes in these patients. NCI also continues to track incidence and survival of women diagnosed with clear cell adenocarcinoma through its Surveillance, Epidemiology, and End Results Program. An ongoing NCI-sponsored initiative is providing information and recommendations to women exposed to DES, their families, and health care professionals. Five regions of the United States are covered in this program, including California, Massachusetts, Texas, and Wisconsin as well as Long Island, New York.
Prostate Cancer	
8. "The Committee expects NCI to expand all facets of prostate cancer research, focus on including investigator initiated research projects, SPORE's, intramural studies, and clinical trails. The Committee also encourages NCI to establish stronger links between its clinical prostate cancer research and NIDDK's basic prostatic science program." (page 81)	8. NCI has expanded all aspects of prostate cancer research in order to pursue basic studies at the molecular level, screening efforts and new therapeutic initiatives. These expanded research efforts will be supported by a variety of funding mechanisms, including investigator-initiated research project grants and intramural studies. NCI has planned two large-scale screening trials in prostate cancer: the PLCO trial seeks to determine whether PSA levels and rectal examinations are effective screening methods for reducing mortality rates and the PIVOT study will compare the effectiveness of surgical intervention vs. "watchful waiting" and palliative management in men with localized prostate cancer. In addition, NCI works in concert with the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK), and is providing funds to support increased efforts in prostate cancer research through the NIDDK O'Brien Urologic Centers.

Item	Action Taken or to be Taken
Proton Beam	
9. "The Committee believes that this research should be continued based on the results to date. The bill includes sufficient resources to finance the next stage of this research initiative." (page 81)	9. In 1993, NCI awarded a $7 million grant to the Massachusetts General Hospital for the initial construction phase of a proton beam facility to provide patients access to this treatment modality. NCI will continue its support for proton beam research.
Coordination	
10. "The Committee urges the NCI to work with the CDC and other PHS agencies to develop a program of coordination to insure the best utilization of Federal resources for cancer research and control activities." (page 81)	10. NCI recognizes the need for close coordination among Federal agencies to achieve mutual goals. In conjunction with the Centers for Disease Control and Prevention (CDCP), NCI will develop and implement the Breast Cancer Action Plan. In addition, the National Strategic Plan on Breast and Cervical Cancer was developed jointly with the CDCP and the Food and Drug Administration (FDA), along with over 150 representatives of Federal/State/local agencies and voluntary and professional groups to guide the coordination and implementation of breast and cervical cancer screening. NCI is the lead agency for the Healthy People 2000 Objectives for cancer and coordinates activities across the Department of Health and Human Services as well as voluntary organizations such as the American Cancer Society. CDCP also has major involvement in this effort and joint and complementary activities between the NCI and CDCP are discussed on a regular basis. In addition, complementary staff expertise and consultation between CDCP and the NCI occur on a regular basis on a variety of topics. NCI also collaborates with the CDCP in making Surveillance, Epidemiology and End Results (SEER) data tapes available to State Health Departments and other interested organizations. A state Tobacco Prevention and Control Network, staffed by the Association of State and Territorial Health

Item	Action Taken or to be Taken
	Officials (ASTHO), has been developed and is jointly funded by NCI, the Office on Smoking and Health (OSH) of the CDCP, and the National Heart Lung and Blood Institute (NHLBI). The purpose of this network is to promote the exchange of information between states on tobacco control activities and to increase coordination of these activities among state health departments.
FY 1994 Conference Report Breast Cancer	
1. "The conferees direct the National Cancer Institute and the National Institute of Environmental Health Sciences to become more aggressive in the pursuit of research into the role environmental factors play in contributing to elevated rates of breast cancer such as have been observed in Nassau and Suffolk counties, in the State of New York, and in other counties throughout the United States. In prohibiting funding for section 1911(d) of P.L. 103-43, it is not the intention of the conferees to prohibit the conduct of the study described in section 1911(a) through 1911(c). The conferees strongly encourage such research into the role of environmental factors and note that the National Cancer Institute retains the discretion to use funds appropriated under this Act to carry out the study so described." (page 23)	1. In response to Public Law 103-43, NCI, in collaboration with NIEHS, initiated the Long Island Breast Cancer Study Project in November 1993. The study will assess biological markers for environmental and other potential risk factors that contribute to the incidence of breast cancer in Nassau, Suffolk, and Schoharie counties in New York and Tolland County in Connecticut. A geographic system will be used to evaluate current and past exposure of individuals to contaminated drinking water, sources of indoor and outdoor ambient air pollution, electromagnetic fields, pesticides, hazardous waste, and other factors. In March 1993, the NCI issued a Request for Applications for studies on environmental factors and breast cancer in high-risk areas including Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont and Washington, D.C. NCI and NIEHS are co-funding these cooperative agreements which will enable scientists in several institutes to cooperate in a large-scale multidisciplinary investigation utilizing a broad diversity of resources and approaches.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Estimate
Research and Investigation..	Section 301	42§USC241	Indefinite		Indefinite	
National Cancer Institute.......	Title IV, Part A	42§USC284c	Indefinite	$1,831,319,000	Indefinite	$1,929,168,000
	(Sec. 408 (a)(1)(A))		Indefinite	(1,685,560,000)	Indefinite	(1,732,030,000)
	(Sec. 408 (a)(1)(B))		Indefinite	(145,759,000)	Indefinite	(197,138,000)
National Research Service Awards..	Section 487(d)	42§USC288	$400,000,000	37,491,000	Such sums as necessary	38,541,000
Total, Budget Authority				1,868,810,000		1,967,709,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Appropriation History

	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1986..........	$1,126,012,000	$1,221.590,000[2]	$1,271,555,000	$1,258,159,000
1986 Sequester				-53,868,000
1987	1,158,089,000[3]	1,346,751,000[3]	1,397,250,000[3]	1,402,837,000
1988..........	1,302,823,000	1,448,411,000[4]	1,527,054,000	1,469,327,000
1989..........	1,468,256,000[5]	1,593,536,000	1,591,036,000	1,571,879,000
1990..........	1,494,741,000[6]	1,652,666,000	1,668,473,000	1,657,161,000[7]
1990 Sequester				-22,829,000
1991..........	1,694,059,000	1,749,392,000[8]	1,747,462,000	1,714,784,000[9]
1991 Sequester				-22,000
1992..........	1,810,230,000	1,830,509,000	2,010,230,000	1,962,587,000[10]
1993..........	2,010,439,000	1,998,616,000	2,010,439,000	1,981,351,000[11]
1994..........	2,142,122,000	2,082,267,000	2,082,267,000	2,082,267,000
1995..........	1,967,709,000[12]			

[1] Reflects enacted supplementals, rescissions and reappropriations.

[2] Excludes $37,358,000 for construction activities and NRSA training programs not considered.

[3] The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes, including $61,674,000 for NCI.

[4] Excludes funding for AIDS research. Proposed to be at the Secretary's level.

[5] Excludes funds for AIDS research and education [$125,280,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

[6] The 1990 request excludes funds for the National HIV program [$151,332,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

[7] Excludes enacted administrative reduction of $6,839,000.

[8] Excludes $35,793,000 for NRSA training programs not considered.

[9] Excludes enacted administrative reductions of $42,568,000 and $8,972,000.

[10] Excludes enacted administrative reductions of $22,255,000, $482,000 and $3,954,000.

[11] Excludes enacted administrative reductions of $16,060,000; $9,933,000; $139,000.

[12] The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Budget Authority by Activity

National Cancer Institute
(dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Research:												
Cancer causation.......	691	$428,850	724	$490,640	715	$492,322	659	$493,752	634	$505,623	-25	+$11,871
Detection and diagnosis research.............	188	117,213	206	121,299	202	134,339	182	135,677	175	146,916	-7	+11,239
Treatment research.....	867	455,364	943	549,954	937	550,568	855	551,764	833	557,966	-22	+6,202
Cancer biology.........	445	287,955	462	286,996	459	301,111	425	299,071	410	309,839	-15	+10,768
Subtotal, research.....	2191	1,289,382	2335	1,448,889	2313	1,478,340	2121	1,480,264	2052	1,520,344	-69	+40,080
Resource Development:												
Cancer centers support.	15	107,649	14	141,468	18	143,647	18	151,936	18	162,944	---	+11,008
Research manpower development..........	31	55,257	40	64,360	35	62,899	34	64,107	34	67,010	---	+2,903
Construction...........	3	7,689	4	12,273	4	7,846	4	18,694	4	12,697	---	-5,997
Subtotal, resource development..........	49	170,595	58	218,101	57	214,392	56	234,737	56	242,651	---	+7,914
Cancer prevention and control..........	198	90,798	225	114,913	231	112,579	223	153,809	223	204,714	---	+50,905
Subtotal, obligations..	2438	1,550,775	2618	1,781,903	2601	1,805,311	2400	1,868,810	2331	1,967,709	-69	+98,899
Unobligated balance lapsing.............		2		16		80		---		---		---
Total, budget authority	2438	1,550,777	2618	1,781,919	2601	1,805,391	2400	1,868,810	2331	1,967,709	-69	+98,899

Justification

National Cancer Institute

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2601	$1,805,391,000	2400	$1,868,810,000	2331	$1,967,709,000	-69	+$98,899,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Cancer Institute. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

This is a time of significant progress in cancer research, including findings that prepare the way for new prevention strategies, diagnostic tests, and treatments. For some cancers--colon cancer, for instance--the insights of basic research have brought an array of advances that, when fully applied, could help save the lives of many Americans who will die of colon cancer each year. Just this year, a gene called MSH2 was identified. This gene is involved in as many as 1 in 6 colon cancers, as well as in some uterine, gastric, pancreatic, bladder, ovarian, and possibly, breast cancers. Another genetic mutation that predisposes individuals to a rare, inherited type of colon cancer, known as familial adematous polyposis (FAP), now can be detected by a blood test that could eventually be adapted for wider screening. Additionally, an NCI study confirms the value of removal of precancerous growths, known as polyps, showing a 90 percent reduction in the risk of colon cancer. These new advances combined with previous research showing that fiber in the diet reduces polyps are pointing to new prevention strategies for this malignancy.

The importance of finding genes linked to specific cancers cannot be overstated. Since the first tumor suppressor genes and oncogenes were identified almost 20 years ago, scientists have sought other genes of critical significance in specific cancers. Tests for inherited diseases are very important because they can reassure some individuals and establish that others need extra vigilance or targeted prevention, intervention, or treatment strategies.

Despite these advances, a number of cancers are on the rise, notably prostate, breast and lung cancers, all of which remain a terrible burden for the American people. So while there is hope-giving progress, we must have no illusions about what remains to be done or how difficult the task will be. The NCI foundation stones of basic cancer research, clinical trials and a nationwide network of cancer centers provide the basis for new laboratory discoveries and a rapid translation to the clinical trials needed to improve cancer care in the community. Gene therapy provides one example of how this process works. The foundation for this therapy was laid over 20 years of research in genetics, immunology and biotechnology. Each small piece of the puzzle had to be fitted together to create this new experimental approach to cancer prevention or treatment. Many laborious studies had to be performed to assure the safety of gene therapy. A new advisory structure had to be created. And then, in August 1990, two little girls with a serious, genetically determined immune disorder were treated with gene therapy. They have continued to do well and are now attending school. This pilot study was the result of teamwork involving NCI and the National Heart, Lung and Blood Institute. Today, nearly 70 gene therapy protocols have been approved.

Now gene therapy techniques are being used to treat not only melanoma, kidney cancer, small cell and non-small cell lung cancer, ovarian and breast cancers, neuroblastomas, glioblastomas, and various lymphomas and leukemias but also other serious diseases, such as immune disorders and cystic fibrosis. And there is an ever widening array of gene therapies. For instance, in treating brain tumors, a retroviral vector is used to slip the gene for herpes simplex thymidine kinase into the brain to be taken up by the tumor cells as they divide. Then the patient is treated with an antiviral ganciclovir which will kill the now altered tumor cells. Twenty patients are being treated and there are plans to treat 20 more patients.

Gene therapy also is being planned for AIDS. Currently, NCI and the National Institute of Allergy and Infectious Diseases have completed preliminary studies on 12 AIDS patients, each with an uninfected identical twin. T-cells from the healthy twin have been infused into the AIDS patients to learn how normal T-cells survive in immunocompromised AIDS patients. This study is a prelude to gene modification studies that could create an entirely new form of treatment for AIDS.

Throughout medical history, vaccines against certain bacteria and viruses have protected against deadly infectious diseases. There are similar hopes for cancer vaccines. A new vaccine combines the gene for carcinoembryonic antigen (CEA) with vaccinia virus. To date, 20 patients with gastrointestinal, breast or lung cancer have been inoculated with CEA-vaccinia vaccine. In another approach, p53, a mutated tumor suppressor protein, is used as a vaccine to stimulate killer T cells which attack the tumor. We do not know if these approaches will work, but, at the very least, this research will lead to new, improved vaccine strategies.

NCI scientists are bringing the insights and skills of basic research to the field of epidemiology and are examining the effects of environmental and occupational exposures as well as the interaction between heredity and environment. Environmental factors, including hormones, dietary factors, and viruses that play a role in the development of cancer, are being studied intensively, including issues of high public concern such as radon, electromagnetic fields, and cellular telephones. Other research addresses the effects of diagnostic and therapeutic radiation and occupational exposures. Chernobyl clean-up workers are also being followed.

Breast cancer rates in the Northeast, specifically on Long Island, and in the mid-Atlantic states are high, and a comprehensive research program is being planned to explore the reasons for these high rates. The Long Island Breast Cancer Study Project is looking at the various factors contributing to breast cancer, including complex and multiple environmental exposures. Factors such as electromagnetic exposures, water, airplane exhaust, organic solvents, polychlorinated biphenyls (PCB) and polybrominated biphenyls (PBB), pesticides, herbicides, heterocyclic amines, and others will be examined in conjunction with case-controlled studies of women in the community. Current exposures and histories of previous exposure will also be measured. Because modern agriculture practice has relied heavily on chemicals, farmers are experiencing high incidence rates of some cancers. A major epidemiologic study of this possible relationship is being carried out by NCI, the Environmental Protection Agency and the National Institute of Environmental Health Sciences. About 100,000 farm workers and their families are being studied to determine the etiologic contributions of pesticides, chemicals, viruses, and other exposures. The contribution of cooking practices also will be evaluated.

Prevention of cancer is of vital importance, and NCI has allocated nine percent of its budget to the cancer control line alone. NCI's investment in women's health and in cancers where the incidence is rising, such as breast and prostate cancer, speaks to the need for cancer prevention and control. There is an urgent need to lower cancer mortality rates, particularly for breast and prostate cancer, in African-Americans.

One environmental and lifestyle issue has been conclusively linked to a carcinogen--tobacco use--yet, lung cancer continues to end lives and devastate American families. About one-third of all cancer deaths are linked to tobacco use. NCI addresses these cancers through basic research on carcinogenesis as well as smoking control programs such as the American Stop Smoking Intervention Study (ASSIST) conducted with the American Cancer Society and state health departments. ASSIST will reach more than 91 million people in 17 states. More men are recorded as former smokers than as current smokers, but more than 43 million Americans still smoke.

To improve the American diet and to reduce the risk of cancer, NCI collaborates with the 5 A Day for Better Health campaign to encourage the intake of more fruits and vegetables, thereby increasing fiber and vitamins and decreasing the fat in the diet. Other programs focus on a specific audience and address many lifestyle factors. These include the National Black Leadership Initiative on Cancer, the National Hispanic Leadership on Cancer, and the Appalachian Leadership on Cancer.

Chemoprevention and bionutrition are becoming important strategies for preventing and treating cancer. Vitamin A-related agents, such as the retinoids and beta-carotene, have been shown to be effective in preventing second head and neck tumors. A recent chemopreventive trial in China demonstrated that adding beta-carotene, vitamin E and selenium to the diet of a malnourished population brought a 13% reduction in the mortality rate from gastric and esophageal cancers. The Prostate Cancer Prevention Trial and the Breast Cancer Prevention Trial are both well under way. Both trials will include genetic analysis of biopsies to explore both inherited and acquired genetic mutations.

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In the future, screening for cancer will undoubtedly rely on molecular tests, but until this is possible, NCI is stimulating research on other new diagnostic tools and on better use of existing tests. While mammography definitively reduces mortality in women over age 50, the same benefit has not been demonstrated for younger women as a group. Thus, there is a serious need for new and better methods to detect early tumors in young women. Digital mammography methods may offer more accurate detection of breast cancer, with better images, less radiation and the potential for electronic image transfer. In some studies, magnetic resonance imaging is being used to explore new ways of screening women for breast cancer. A totally new approach, electron spin resonance (ESR) imaging, which attempts to develop images of free radicals based on electron spin (paramagnetic) strategies, is in an early design and testing phase.

Screening tests for prostate, lung, colorectal, and ovarian cancers are being studied in PLCO, a large clinical trial. About 37,000 men and 37,000 women will be enrolled with equal numbers of men and women followed as a control group. This study will assess the predictive value of such tests as PSA, ultrasound, and CA125. The study also use biopsies to determine genetic alterations and to develop biomarkers to pinpoint early cancers.

Cancer patients have benefitted from the investment of the Congress in NCI's drug development program. NCI scientists have discovered or contributed to the development of the majority of cancer drugs now approved by the FDA. Taxol®, pentosatin, fludarabine, and deoxycoformycin have been approved within the last two years. Taxol is approved for ovarian cancer and is expected to be approved for breast cancer. Currently, Taxol is being tested in various combination therapies, and research continues on such analogues as Taxotere and semi-synthetic and synthetic versions. More than 200 agents are in preclinical development.

NCI's investment package in high-speed computing is directed toward rational drug design. Other computing efforts will benefit the expansion of PDQ, the Institute's computerized database on cancer and cancer treatment.

A relatively recent approach to cancer treatment has been to interrupt the basic processes of the malignant cell: its ability to signal other cells, to invade other tissues, or to stimulate the blood supply the tumor needs to expand. Since treatment of primary tumors is quite successful and since most cancer deaths occur when the tumor spreads, blocking that spread, called metastasis, would be an important advance in the treatment of many cancers. Now, CAI, a metastasis-blocking agent, is in clinical trials. Inhibiting new blood vessel formation (angiogenesis) could reduce metastasis and tumor growth, particularly in brain tumors. Angiogenesis is heavily involved in the development of AIDS-related Kaposi's sarcoma.

Throughout the National Cancer Program, swift transfer of knowledge from the laboratory to the bedside is of prime importance. NCI emphasizes the translation of basic research into prevention and treatment clinical trials. The Specialized Programs of Research Excellence (SPOREs) in breast, prostate, lung and, most recently, gastrointestinal cancers encourage interdisciplinary research and focused scientific training on these cancers.

NCI scientists are developing treatments based on monoclonal antibodies to home in on cancer cells and to kill them. One experimental treatment using a monoclonal antibody chemically bonded to a form of the pseudomonas exotoxin is in early clinical trials for patients with metastatic breast cancer, carcinoma of the colon metastatic to the liver and the lungs, and other widely disseminated tumors. A monoclonal antibody has been directed against a growth factor receptor to treat a form of aggressive T-cell leukemia--adult T-cell leukemia (ATL)--caused by the human retrovirus HTLV-I. This research is in an early experimental form but offers hope in a disease where there is currently no curative treatment. Another monoclonal antibody is engineered to target the protein product of the HER-2/neu oncogene and at the same time to deliver radiation to the HER-2/neu-positive cells and will aid in diagnosis of and eventually in treatment of breast and, perhaps, ovarian cancers.

NCI is proud of its pioneering program of information dissemination to patients, the public, scientists, and health care providers. The Cancer Information Service answers 600,000 calls annually and has increased its outreach services. The International Cancer Information Center distributes information on cancer research, diagnosis, and treatment through PDQ, CancerNet, CancerFAX, and other programs. The Journal of the National Cancer Institute has become an important publication to bring new advances in cancer to the international scientific community.

NCI has an investment package of approximately $10 million in AIDS research, in addition to its standing base. NCI scientists have determined that cell-mediated immunity is present in some individuals who have remained healthy despite exposure to HIV. This observation presents a very promising research direction, with potential for the development of an AIDS vaccine. Women are increasingly being infected with the virus and perinatal transmission to the infant is a very serious problem. One study of twins suggests exposure in the birth canal is involved in transmission of the virus; an intervention trial is being designed to test an inexpensive viricidal solution to cleanse the birth canal to lower the risk of infection during delivery.

From the beginning of the AIDS epidemic, NCI epidemiologists have collaborated with scientists in other nations, particularly in Africa and the Caribbean, monitoring populations infected by HIV and those at high risk. It has been possible, through molecular epidemiology, to isolate and identify various strains of the AIDS virus, including those most prevalent in the United States, which has helped in vaccine development. To find promising agents against AIDS, NCI has tested more than 137,000 agents in an AIDS drug screen, including a number of natural products. The NCI AIDS drug screen is a national resource.

In conclusion, although there are important achievements including genetic discoveries, genetic tests, vaccines, gene therapy, innovative biotechnology, prevention approaches, and an insight into cell-mediated immunity to HIV, there should be no illusions as to the challenge. The broad NCI research programs in basic genetics, cancer biology, carcinogenesis, epidemiology, diagnosis, treatment, and prevention, plus the multifaceted contributions of the cancer centers to all disciplines of cancer research and clinical application, are all needed to complete the task of preventing or curing cancer and AIDS. There is no doubt that cancer represents one of the most formidable challenges in science and medicine today.

The President's appropriation request of $1,967,709,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Cancer Institute during the last five years has been as follows:

	Amount	FTE
FY 1990	$1,493,115,000	2,271
FY 1991	1,550,777,000	2,438
FY 1992	1,781,919,000	2,618
FY 1993	1,805,391,000	2,601
FY 1994	1,868,810,000	2,400

Purpose and Method of Operation

The NCI supports cancer research through several major scientific approaches. Cancer causation research includes investigations into the fundamental causes of human cancer and includes studies in chemical and physical carcinogenesis, biological carcinogenesis, epidemiology, chemoprevention and nutritional research. Detection and diagnosis research includes studies designed to improve diagnostic accuracy, characterize the behavior of tumors and predict the course of disease, and to identify individuals at increased risks for particular cancers. Treatment research spans both preclinical and clinical research and includes innovative approaches to cancer treatment and the application of the traditional modalities of surgery, chemotherapy and radiation therapy. Cancer biology supports a wide spectrum of basic research and attempts to understand the details of how cancer grows and spreads. Cancer centers support provides core funding to cancer research centers located across the nation and supports a diversity of research approaches to the problem of cancer. Additionally, the newly established Specialized Programs of Research Excellence (SPOREs) provide funding to institutions to concentrate on laboratory and clinical approaches for major cancer sites. Research manpower development strives to ensure an adequate supply of cancer researchers. The Construction program permits the development of facilities required for cancer research. Cancer prevention and control research emphasizes the translation of research knowledge into health promotion and disease prevention activities for the benefit of the public.

Overall Budget Policy

The FY 1995 budget request for the NCI is $1,967,709,000 an increase of $98,899,000 over the FY 1994 comparable amount of $1,868,810,000.

The $1,967,709,000 for cancer research is an increase of 5.3% over 1994 and includes targeted increases in breast cancer research and high performance computing. The FY 1995 NCI funding for breast cancer research will increase by $60,703,00 to a level of $323,650,000 which is an increase of 23% over the FY 1994 level. The Cancer Prevention & Control budget will increase to nine percent of the total NCI budget in accordance with Sec. 417 of Public Law 103-43. Research Project Grants will remain a top priority of the Institute and this budget will provide for 1,052 competing awards, an increase of 205 grants over the comparable FY 1994 level. In addition, $12,016,000 of decreases associated with administrative costs and FTE reductions associated with cancer research have been incorporated.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. Average costs of competing research project grants would receive an increase equal to the Biomedical Research and Development Price Index (BRDPI) of 4.1 percent.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Research

1995 Authorizing Legislation - Section 301 of the Public Health Service Act. Title IV, Part A, Section 408(a)(1)(A) and Section 408(a)(1)(B) of the National Cancer Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
2313	$1,478,420,000	2121	$1,480,264,000	2052	$1,520,344,000	-69	+$40,080,000

PROGRAM ACTIVITY:	FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
Cancer causation...	659	$493,752,000	634	$505,623,000	-25	+$11,871,000
Detection and diagnosis........	182	135,677,000	175	146,916,000	-7	+11,239,000
Treatment research.	855	551,764,000	833	557,966,000	-22	+6,202,000
Cancer biology.....	425	299,071,000	410	309,839,000	-15	+10,768,000
Total............	2121	1,480,264,000	2052	1,520,344,000	-69	+40,080,000

MECHANISM:	FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Research projects..	3230	$906,339,000	3233	$936,190,000	+3	+$29,851,000
Other research:						
Cooperative clinical research........	232	77,233,000	233	78,955,000	+1	+1,722,000
Minority biomedical research support..		3,099,000		3,223,000		+124,000
Other research related..........	287	13,031,000	312	14,491,000	+25	+1,460,000
Subtotal, other....	519	93,363,000	545	96,669,000	+26	+3,306,000
Total, rsrch grants	3749	999,702,000	3778	1,032,859,000	+29	+33,157,000
Research and development contracts..	235	124,693,000	245	125,221,000	+10	+528,000
Intramural research		280,974,000		286,183,000		+5,209,000
Research management and support......		74,395,000		75,026,000		+631,000
Cancer prevention and control...........	3	500,000	6	1,055,000	+3	+555,000
Total, NCI........		1,480,264,000		1,520,344,000		+40,080,000

Funding for the Research budget activity during the last five years has been:

	Amount	FTE
FY 1990............	1,244,294,000	2,039
FY 1991............	1,289,384,000	2,191
FY 1992............	1,448,905,000	2,335
FY 1993............	1,478,420,000	2,313
FY 1994.............	1,480,264,000	2,121

CANCER CAUSATION RESEARCH

Cancer causation research investigates chemical and physical carcinogenesis, biological carcinogenesis, epidemiology, chemoprevention, and nutrition. Research findings in any one of these areas may shed light on a problem being investigated in another, for ultimately each discipline is concerned with the fundamental causes and prevention of human cancer.

Rationale for the Budget Request

The FY 1995 request of $505,623,000 represents an increase of $11,871,000 from the FY 1994 estimate. Efforts are supported through an Intramural Research program conducted by Federal scientists integrated with an comprehensive Extramural Research effort conducted by NCI grantees and contractors. The program plans for FY 1995 are as follows:

The Multistage Process of Cancer Development

Carcinogenesis is a multistage process driven by carcinogen-induced genetic and non-genetic (epigenetic) damage in susceptible cells that gain a selective growth advantage and undergo clonal expansion as the result of activation of proto-oncogenes and/or inactivation of tumor suppressor genes. These stages include tumor initiation, tumor promotion, progression, and finally invasion and metastasis. The numerous steps involved in the carcinogenic process offer opportunities to intervene at several stages of the process of transformation of a normal cell to a cancer cell.

Hormonal Carcinogenesis - Intramural and Extramural Research

More than 25 percent of human tumors originate in endocrine tissues or their target organs. However, the precise way in which hormones affect cell transformation remains unclear. Tissues such as breast, ovary, endometrium and prostate are dependent upon an interactive network of steroid hormones (estrogens, progestins, androgens) for their structural and functional development and, to a large degree, the proliferation of specific cell types within those tissues is hormone-driven. The definition of the relationship between the level and duration of hormone exposure to other endogenous and exogenous factors and malignant transformation in such hormonally-sensitive tissues is an important focus of hormonal carcinogenesis research. In addition, diverse tissues (e.g. breast and prostate) are likely to have substantial common ground in the transformation process.

Heterocyclic Amines and Cancer - Extramural Research

Nineteen heterocyclic amines (HCAs) have been identified in meat, fish, and fowl cooked at high temperatures, i.e. broiling, frying, or grilling. Recently, lower levels of HCAs have been identified in overbaked bread products containing wheat gluten. Nine of the HCAs have been synthesized and found to be carcinogenic in rodents. The most abundant HCA in cooked meat -- PhIP -- causes breast and colon cancer in rats.

Intramural Research:

In a certain strain (Sprague-Dawley) of female rats, PhIP induces breast cancer within three months and has been found in mammary milk, thereby exposing the nursing pups. During the next year, studies will focus on evaluating HCA intake and their risk to humans, along with other potential adverse effects, as well as methods to mitigate their formation and/or absorption.

Environmental Radiation Exposure - Intramural and Extramural Research:

Radiation exposure studies are being conducted to provide new information on the mechanisms by which cancer is produced and to provide guidance on approaches to cancer prevention through exposure avoidance. Studies include important public health concerns, such as electromagnetic fields, cellular telephones and indoor radon. Cancer risk is also being studied in patient populations exposed to diagnostic and therapeutic radiation, occupational groups, and special groups like the Japanese A-bomb survivors. New studies of women with lung cancer in Missouri will provide important information on lung cancer risk due to residential radon. Childhood leukemia risk and electromagnetic exposures from household electric power supplies is being assessed. Brain cancer is being evaluated in relation to microwave exposures from cellular telephones, and all cancers in relation to occupational exposures to radar during the Korean War. Medically-irradiated populations are also under study for quantitative estimates of radiation risks. Tumor specimens from A-bomb survivors and other exposed groups are being evaluated to identify possible characteristic mutations. Chernobyl clean-up workers are being studied in the Baltic countries, a similar study is soon to be initiated in the Ukraine, and negotiations are underway to study thyroid cancer among children in Belarus exposed to radioactive iodine released by the accident.

Viruses and Cancer - Extramural Research

Three of the large DNA tumor viruses, Epstein-Barr virus, adenovirus and Herpes simplex virus 1, have been found to contain different genes which block the normal cellular process of programmed cell death (apoptosis). These three viruses share a common pathway in cell transformation, and also provide model systems in which to study the general role of apoptosis in tumorigenesis. New lines of transgenic mice containing EBV genes have recently been established. This new animal model will enhance studies on the role of an EBV protein in lymphomagenesis. Several new growth-regulatory genes and oncogenes have been discovered. Studies of their mechanism of action and patterns of expression should lead to the development of better diagnostic markers and treatments for epithelial cell and hematopoietic tumors. The newly discovered oncogenes may make attractive targets for devising anti-tumor therapeutics.

Mouse mammary tumor virus (MMTV) is a retrovirus that induces breast cancer in mice. Virus particles are secreted into the milk, from which they are absorbed by suckling pups. It was recently discovered that MMTV produces a superantigen which induces a T-cell response (probably proliferation) that transmits the virus from the gut of newborn mice to mammary gland cells, where the virus induces tumors. Recent experiments in which the MMTV superantigen was inserted into transgenic animals before birth suggest that it may be possible to immunize against some viral infections or virally-induced tumors before birth by exposure of a fetus to specific viral proteins.

Cancer Vaccines - Intramural and Extramural Research

The development of preventive or therapeutic human cancer vaccines is one of NCI's highest priorities. The human papillomaviruses, hepatitis viruses, and the Epstein-Barr virus have been linked with various human cancers and vaccine development efforts are planned or ongoing for these viruses. Since lung cancer has the highest cancer death rate in the United States, molecular markers are needed to detect malignant lung cancer at an early stage to permit successful therapeutic interventions. Scientists have examined gene products expressed differentially in small cell lung cancer cells and in normal cells. A clone from a lung cancer cell line now being studied might possibly prove useful as a biochemical marker for certain stages of human small cell lung cancer. Additionally, tumor-specific markers may be used as antigens for cancer vaccines or for the generation of antibodies that could be conjugated (linked) with toxins for therapeutic use. Other ongoing efforts involve a Phase I clinical trial of a recombinant CEA-vaccinia construct in patients with adenocarcinoma of the gastrointestinal tract, breast and lung.

Women's Cancers - Intramural Research

Analysis of a case-control study among younger women will focus on breast cancer risk and oral contraceptive use, diet (including during adolescence), alcohol consumption, and other etiologic hypotheses. Studies will explore the reasons for the differential incidence of breast cancer in white and African American women. Other research will examine risks and benefits of menopausal hormone replacement therapy among older women and the potential role of environmental agents (e.g., pesticides) in breast cancer.

Intramural and Extramural Research:

In March 1993, the NCI issued a Request for Applications for multidisciplinary studies on environmental factors and breast cancer in high-risk areas including Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont and Washington, D.C. Also, in response to Public Law 103-43, NCI, in collaboration with National Institute for Environmental Health Studies, initiated the Long Island Breast Cancer Study Project in November 1993 to assess biological markers of environmental and potential risk factors contributing to the incidence of breast cancer in Nassau, Suffolk, and Schoharie counties in New York and Tolland County in Connecticut. A geographic system will be used to evaluate current and past exposure of individuals to contaminated drinking water, sources of indoor and outdoor ambient air pollution, electromagnetic fields, pesticides, hazardous waste, and other potential risk factors. Grantees and intramural staff are currently collaborating in this project. Other studies will continue to evaluate various dietary factors, including caloric intake, fat, and heterocyclic amines and their potential role in breast cancer risk.

Several interdisciplinary studies of ovarian and endometrial cancer are underway to examine potential ways to prevent these malignancies. Studies will include major efforts to examine the influence of endogenous hormones, dietary factors and genetic susceptibility. Several large efforts will investigate the progression of human papillomavirus cervical lesions, including the influence of host and exogenous factors in Portland, Oregon and Costa Rica (where the cervical cancer incidence is approximately six-times that of the U.S. rate). A large retrospective study will address the long-term health effects of silicone in cosmetic breast implants and the ability to detect breast lesions in women with implants. Another study will evaluate cancer risks associated with infertility (including certain hormonal deficiencies) in women, as well as types of treatment.

Cancer in Minorities - Intramural and Extramural Research

Studies are investigating the high rates of multiple myeloma and cancers of the pancreas, esophagus, and prostate in African Americans. Analysis of record-based and questionnaire data for risk factors will continue, while laboratory assays on biological specimens seek to identify hormonal or genetic biomarkers associated with risk. A case-control study will attempt to determine why breast cancer rates in premenopausal African American women are higher than for white women. A pilot study of Adult T-cell leukemia/lymphoma (ATL) in the Crown Heights section of Brooklyn, New York will investigate its prevalence and clinical patterns in the African American population. NCI, along with the Indian Health Service, will begin a pilot project using new techniques to measure human papillomavirus infection in Native American women to improve early detection. The Alaskan Native American Cancer Registry will be used to investigate the molecular epidemiology of several other virus-associated malignancies (e.g., lymphoma, liver cancer and nasopharyngeal cancer). A case-control study has begun to assess the role of alcohol, tobacco, diet, personal hygiene (including mouthwash use), HPV infection, and other factors, and the high oral rates cancer found in Puerto Rico.

Environmental and Occupational - Intramural and Extramural Research

Approximately 50,000 farmers and their families from Iowa and North Carolina will be followed in a collaborative project involving the National Institute of Environmental Health Sciences and the Environmental Protection Agency for ten years or more to relate cancer and other disease risks with agricultural work and other aspects of rural life. The project will monitor numerous environmental exposures, identify biologic markers for exposures, and investigate the role of environment, occupation, and diet, including intake of heterocyclic aromatic amines (products formed in well-cooked meat), in the etiology of lung, colon, prostate and breast cancer. Another project will determine the most feasible research design to obtain information on cancer patterns and risks for migrant and seasonal workers who are exposed to pesticides during agricultural work. Others studies will investigate cancer risks of pesticides among lawn care maintenance workers and agricultural herbicide applicators.

Case-control studies of various cancer types will assess risks associated with a variety of occupational exposures, including organic solvents, dusts, engine exhausts and pesticides. Cohort studies will focus on aircraft maintenance workers exposed to degreasing chemicals; dry cleaners exposed to organic solvents; furniture workers exposed to wood dusts, paints and varnishes; fire fighters exposed to combustion products; smelter workers exposed to arsenic; and chemical workers exposed to formaldehyde and acrylonitrile. Biological specimens will be collected to investigate markers for exposure, genetic susceptibility and mechanisms of carcinogenesis.

Genetic Epidemiologic Studies and Cancer - Intramural and Extramural Research

Families prone to breast and ovarian cancer will be studied to isolate the gene for these malignancies, as well as to assess the psychosocial implications of genetic screening and to develop guidelines for clinical management of family members. Work will continue on the mapping of genes for melanoma, including isolating genes on chromosomes 1p and 9p. Families with dysplastic nevi, a precursor for melanoma, will also be evaluated since there may be several genes important in the development of both dysplastic nevi and melanoma. Families with Hodgkin's disease will be evaluated to assess the genetic and environmental components of risk, and linkage analyses conducted to search for a gene associated with the disease. Studies will continue to investigate specific mutations in the neurofibromatosis 2 (NF2) gene and clinical presentations of the disease, while other efforts will examine the relationship of the gene to familial meningioma (a benign brain tumor). Other genetic epidemiologic studies will evaluate families with Li-Fraumeni syndrome, chronic lymphocytic leukemia and cancers of the bladder and testes.

Nutrition Studies - Intramural and Extramural Research

Scientists are studying the role of total calories, specific fatty acids, vegetables, fruits, fiber and environmental agents (e.g., pesticides, heterocyclic amines), as well as childhood and adolescent diet, as potential risk factors for breast cancer. Emphasis will be placed on diet and endogenous hormone levels, body size and shape, weight gain patterns and physical activity. Increased vegetable and fruit intake has been shown to be associated with reduced risk of cancer at many sites. Prospective and retrospective studies will clarify the specific cancer sites affected, the crucial vegetable and fruit subgroups, the importance of raw produce and the degree of risk reduction. The optimal number of servings a day of vegetables and fruit will be estimated by combining national descriptive dietary data with results of epidemiologic analyses. A technique to measure the major individual carotenoids in blood, developed in collaboration with the National Institute of Standards and Technology, is being used to investigate their role in affecting lung and upper digestive tract cancer risk. Elevated lung cancer risk has been associated with low fruit and vegetable consumption, and a recent study of nonsmoking women found increased risk among those who consumed diets rich in saturated fat. A follow-up study will evaluate the relation of diet in women who smoke. Other studies will investigate the importance of nutritional factors in endometrial, cervical and other cancers.

A Broad Program of Information Dissemination - Intramural Research

NCI provides education, outreach programs and state-of-the-art information to the American public and health professionals. The Cancer Information Service (CIS) provides direct access to current information on cancer detection, prevention and treatment toll-free (1-800-4-CANCER) that receives nearly 600,000 calls annually. NCI distributes more than 20 million free publications each year in support of education initiatives. Outreach programs in nutrition, smoking cessation, and mammography screening are conducted nationwide and target specific populations such as older Americans, minorities, and other underserved groups. NCI also conducts patient education outreach programs on clinical trials accrual, cancer pain relief, cancer survivorship, palliative care, and home or hospice-based care.

DETECTION AND DIAGNOSIS RESEARCH

NCI supports research to improve diagnostic accuracy; characterize the behavior of tumors and predict the course of disease; monitor the response to therapy; detect cancer earlier; and identify individuals at increased risk for particular cancers. The accuracy of the diagnosis, including improved classification of tumors, and the precision of pathologic staging are critical to choosing the most effective therapy. Support continues for the rapid transfer of technologies from basic research to clinical application. The need for human tissue resources is being met to capitalize on tumors from well-characterized patient populations with extensive follow-up data.

Rationale for the Budget Request

The 1995 budget estimate of $146,916,000 represents an increase of $11,239,000 from the 1994 estimate. Efforts are supported through an Intramural Research program conducted by Federal scientists integrated with an comprehensive Extramural Research effort conducted by NCI grantees and contractors. The program plans for 1995 are as follows:

Breast Cancer - Intramural and Extramural Research

Breast cancer patients with no apparent involvement of the axillary lymph nodes (node-negative breast cancer) have a generally good prognosis. However, in about 30 percent of these patients, the disease will progress and the patient will die of metastatic disease. Standard prognostic factors (tumor size, histologic differentiation, and age) are used to define groups of node-negative patients with high or low risk for recurrence. Because some patients cannot be easily assigned to either risk group, additional markers are required to aid in making the important decision of which therapy to use. NCI awarded cooperative agreements to develop a breast cancer tissue registry that accesses thousands of archival tissue specimens with extensive follow-up information and makes them available for studies to evaluate new prognostic markers. Continuing support for this resource and for marker validation studies should lead to improved care for breast cancer patients.

A significant fraction of women with estrogen receptor (ER) positive tumors do not respond to hormonal therapy. NCI-supported investigators have identified forms of ER and other molecules that appear to interfere with the normal binding of estrogen to the receptor and with the normal function of the ER. Variant ERs have been detected in human tumor specimens, and it has been shown that they do not interact normally with the cellular DNA. Their analysis may lead to new methods for predicting response to hormonal therapy. NCI-supported researchers will continue studies to identify ER mutations and regulated proteins that may be useful as prognostic markers.

The cellular proliferation rate (the rate at which cells divide) may be a prognostic indicator for breast cancer. High S-phase fraction (the fraction of cells in the DNA synthesis phase of the cell cycle) measured by flow cytometry has been associated with poor outcome. Alternative approaches to measure proliferation include immunohistochemical methods in tumors from patients with node-negative breast cancer. The results will be compared to flow cytometric measurements of S-phase fraction to define the prognostic utility of these measurements in node-negative breast cancer patients.

The prognostic significance of mutations in the p53 tumor suppressor gene that are common in breast tumors has not been established. Evaluation of p53 status in tumors from patients with invasive breast cancer revealed a highly significant correlation between high p53 expression, late stage, the presence of metastatic tumors and low concentration of progesterone receptor. Studies of p53 as a prognostic indicator in node-negative breast cancer are being performed under Master Agreement Orders.

Extramural Research:

Digital imaging of the breast offers advantages in image quality compared to conventional film-based systems: improved image contrast and resolution at a reduced radiation dose; more efficient image storage and retrieval; the potential for electronic image transfer facilitating comparison to previous films and review by expert mammographic readers; and the potential for computer-assisted image interpretation. An interagency agreement between the NCI and the National Aeronautics and Space Administration established the Working Group for Digital Mammography Technology Transfer to identify technologies critical to the development of digital mammography. A program announcement resulted in funding of applications addressing some of the fundamental technologic problems in digital mammography. Multi-disciplinary teams will be formed composed of clinical radiologists, physicists and technical equipment designers from industry and the private sector.

Other Women's Cancers - Intramural and Extramural Research

Most of the cases of ovarian cancer diagnosed annually in the U.S. are at an advanced stage and not amenable to treatment. Markers to allow earlier detection and to predict the course of disease are needed. NCI-supported investigators have been examining chromosomal alterations to better understand the progression of ovarian malignancies from low grade to high grade lesions. Consistent non-random alterations have been found. Genetic alterations occurring in low grade tumors may reflect early changes that may be critical to the development of malignancies and this research will continue to be pursued. Tissue specimens, serum samples, and clinical follow-up data for each patient are being collected in a tissue bank to facilitate important research in ovarian cancer.

NCI has responded to widespread concern about the quality assurance in cervical and vaginal cytology by coordinating the development of the new Bethesda System (TBS) to replace the Papanicolaou (PAP) classification. Guidelines have been developed for examination of specimens from cancer patients. Progress in computer hardware and image interpretation software has led to sophisticated imaging systems to prescreen Pap smears for malignant cells. Pap prescreening systems used in conjunction with TBS for reporting results, and combined with appropriate public health interventions could significantly reduce the mortality from cervical cancer.

Prostate Cancer - Intramural and Extramural Research

The Prostate Research Network was established to identify and characterize cytogenetic and molecular genetic alterations in prostate cancer. The cooperative network is identifying genetic markers that can distinguish the indolent and aggressive forms of prostate cancer and changes that may explain the differences in incidence associated with age and race.

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Progress in Other Important Malignancies - Extramural Research

Results from an NCI-supported large, randomized trial on the effect of periodic screening for occult blood in the stool indicate that colorectal cancer mortality can be reduced by 33% with annual screening. The participants will continue to be followed to evaluate whether screening every other year is also effective and whether removal of colorectal polyps caused a significant reduction in colorectal cancer incidence. The trial included equal numbers of men and women, and continued follow-up will determine whether there are gender-related differences in the effectiveness of screening.

Studies by NCI-supported investigators showed that the expression of the mucin-associated carbohydrate antigen, sialosyl-Tn is associated with poor prognosis in colon cancer patients. Recent studies suggest its expression may be associated with malignant potential and will assess its clinical usefulness in the early diagnosis and management of colorectal cancer.

Incidence and mortality rates for brain tumors continue to rise. The NCI-sponsored Glioma Research Network was established to evaluate molecular probes in an effort to find markers that can better predict the behavior of human gliomas. In addition to developing guidelines for neuropathologists to use existing classification systems more consistently, researchers are evaluating the prognostic importance of particular chromosomal alterations, expression of tumor suppressor genes, and the altered production of cellular glycolipids. The Network will allow more extensive analyses of these markers which should lead to improved treatment of patients with brain tumors.

Approximately 90 percent of lung cancer patients will die of their disease. Retrospective studies of resected Stage I non-small cell lung cancer (NSCLC) patients are underway to determine if a variety of prognostic variables that have been previously described as affecting outcome in NSCLC can predict risk of recurrence. Some of these markers may be useful to identify patients with very early stage or premalignant lung cancer lesions.

Technology Transfer from Laboratory to Clinical Practice - Extramural Research

Progress is being made in the evaluation of prognostic markers by using the polymerase chain reaction (PCR) technique with DNA extracted from paraffin embedded archival tissue. Genetic alterations identified in tumors of various stages and grades can now be correlated with long-term outcome. Because of its sensitivity, PCR is being used to look for genetically altered tumor cells in the bone marrow of patients treated for lymphomas or leukemias. These techniques are much more sensitive than the standard histological evaluation of bone marrow, although the clinical significance of finding a very small number of cells following treatment must be evaluated. These same approaches are being used to search for metastatic disease in lymph nodes and in marrow of patients with solid tumors. This should improve treatment strategies.

Physicians treating patients with early stage bladder cancer do not have adequate markers to predict progression and recurrence in these patients. The NCI-supported Marker Network for Bladder Cancer has developed a protocol to prospectively evaluate a series of markers that have been shown to help predict progression or recurrence. The study will require two years to accrue patients, collect the necessary specimens, and follow the patients.

TREATMENT RESEARCH

Almost 1.2 million Americans will be diagnosed with cancer this year, and most will receive cancer-directed treatment and supportive care during their illness. The NCI has long emphasized the discovery and development of better, safer, more effective treatments for all cancer patients. Advances in our understanding of fundamental processes involved in the development of malignancies have been derived from basic science research, and have resulted in new, innovative approaches to cancer treatment and advances in the application of the traditional modalities of surgery, cytotoxic chemotherapy and radiation therapy.

Rationale for the Budget Request

The FY 1995 request of $557,966,000 represents an increase of $6,202,000 from the FY 1994 estimate. Efforts are supported through an Intramural Research program conducted by Federal scientists integrated with an comprehensive Extramural Research effort conducted by NCI grantees and contractors. The program plans for FY 1995 are as follows:

Natural Product Development - Extramural Research

A primary focus of NCI's drug discovery efforts has been the screening of natural product extracts from a wide variety of plant and marine organisms. The NCI, along with other NIH Institutes, the National Science Foundation, and the U.S. Agency for International Development, established an international program that involves developing countries in drug discovery, the development of inventories of native species and indigenous knowledge, and the training of native scientists. Three international cooperative groups were funded in September 1993 to promote the collection and cataloguing of endangered tropical plant and animal species for further study as well as promote intelligent use of these scarce resources. The NCI maintains the Natural Products Repository at the Frederick Cancer Research and Development Center where natural products are stored, carefully documented, and formulated for testing in cell line-based screens for anti-cancer and anti-HIV activity.

Expanded In Vitro and In Vivo Drug Testing - Intramural Research

NCI's commitment to develop a human tumor cell line screen for disease-oriented in vitro drug testing has resulted in a number of advantages: the automation of the screen to permit a disease specific approach; a re-emphasis on broad based screening of natural products; strategic in vivo testing and drug development; and the development of a "hollow fiber" assay for the rapid assessment of in vivo anti-tumor activity. The hollow-fiber approach is a significant advance in vivo testing whereby a drug can be tested against three different tumor cell lines imbedded in hollow-fibers and implanted simultaneously in both the intraperitoneal cavity and subcutaneous tissue of the mouse. This approach provides a much more efficient use of a drug (often first extracted in milligram quantities) and of experimental animals, permitting an initial assessment to be made in two weeks.

From 1990 through 1992, an estimated 30,000 new synthetic and natural compounds were screened for anti-cancer activity in NCI's intramural drug screen in 60 different human tumor cell lines. Compounds were selected for high priority testing on the basis of a new or unique chemical structure or a pattern of activity, potency, and availability. Of these, over 200 are now in various stages of preclinical testing. Further development of the cell-line screen has focused on its molecular characterization to enhance understanding of the mechanism of action of promising new agents.

Breast Cancer Cell Lines - Intramural Research

In 1988, a specific initiative was undertaken to develop a sub-panel of breast cancer cell lines to assess the specific activity of new agents against breast cancer. This was a significant undertaking due to the technical difficulty in maintaining and characterizing these human-derived breast tumors. A sub-panel composed of 8 human-derived breast cancer cell lines first became operational in December 1992 and 2,000 new compounds previously identified in the NCI drug screen were retested against them. Of these, 91 were identified with specific activity, and 51 compounds were selected for expedited preclinical development. Similar efforts are underway to develop a prostate cancer sub-panel. As a result of the drug development program, a number of new agents with preclinical activity against breast cancer are now entering Phase I/II clinical trials.

Cytokine Development - Intramural Research

One of the most important clinical developments in cancer treatment has been the application of colony-stimulating factors to reduce the magnitude and duration of chemotherapy-induced depletion of white blood cells. Granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage-colony-stimulating factor (GM-CSF) have been shown to hasten white blood cell recovery following chemotherapy and they may permit the use of somewhat higher (and possibly more effective) doses of chemotherapy. Despite these advantages, they have not been shown to exert any favorable effects on platelet counts which generally are also affected by chemotherapy. Recent studies have suggested enhanced platelet recovery with administration of IL-3 and IL-11 and these agents are now in clinical trials. Other promising new factors include PIXY 321, a genetically engineered fusion protein combining IL-3 with GM-CSF and SCF, a factor which stimulates growth of early, multipotent stem cells that are precursors for a variety of blood cells.

New Drugs in Clinical Trials - Intramural and Extramural Research

A number of new drugs have entered early clinical testing both intramurally and extramurally within the past year. These include bryostatin-1, an enzyme inhibitor with activity against acute leukemia cells; taxotere, a semisynthetic analog of taxol developed and initially tested clinically in Europe; anthrapyrazoles; fenretinide (4-HPR), a retinoid capable of inducing differentiation of cancer cells; and camptotecins, inhibitors of the enzyme topoisomerase I with activity against colon cancer cells. Several additional compounds are expected to enter trial in late 1993 or early 1994 including various cytotoxic agents, cytokines and Interleukin-12, differentiation agents, modulation agents, and monoclonal antibodies.

Paclitaxel (Taxol®) Development - Intramural and Extramural Research

Paclitaxel is the first of a new class of anticancer drugs in which tubulin and microtubules are critical targets for chemotherapy. It binds to and stabilizes microtubules and is thought to kill cells by disrupting cell division. Initial Phase I and II studies have shown significant activity in refractory ovarian cancer and in metastatic breast cancer. Recent studies have focused on defining optimal delivery schedules and combination regimens. The first Phase III trial compared paclitaxel plus cisplatin to standard therapy in women who had surgery for their ovarian cancer. Paclitaxel therapy was associated with a significant improvement in clinical response rate and preliminary analysis demonstrated increased patient survival with this treatment. Results of this trial and of three additional Phase III trials now underway will define the role of paclitaxel in primary and refractory ovarian cancer. Because of results from these and other NCI-supported clinical trials, paclitaxel was approved by the FDA in FY 1993 for use in patients with refractory ovarian cancer.

Suramin for Treatment of Metastatic Prostate Cancer - Intramural Research

NCI-sponsored clinical trials have established the efficacy of suramin in the treating patients with hormone refractory prostate cancer. Of thirty patients with metastatic prostate cancer treated with suramin in addition to standard therapy, 70 percent lowered their previously elevated prostate specific antigen (PSA) levels to the normal range, with 50 percent lowering them to undetectable levels. Approximately half of those with measurable soft tissue disease had a response. These results compare favorably to previously reported studies of men with metastatic prostate cancer treated with routine hormonal therapy, where only 22-50 percent normalize their PSAs and 0-30 percent drop to undetectable PSA levels. Normalization of PSA was found to be a good predictor of response: four of the nine patients whose PSA did not fall to the normal range have died. In this trial, suramin was safely administered in the outpatient setting with few toxicities observed. The results of these studies support the conduct of larger randomized clinical trials among multiple extramural investigators to define the role of suramin with total androgen ablation.

Carcinoembryonic Antigen (CEA) Vaccine Clinical Trials - Intramural Research

Carcinoembryonic antigen (CEA) is one of the most widely studied tumor associated antigens. It is expressed by more than 90 percent of gastrointestinal carcinomas, 50 percent of breast cancers, and 70 percent of adenocarcinomas of the lung. While CEA is generally a weak antigen in humans and there is no evidence of humoral or cell-mediated immunity to CEA in normal or cancer patients, CEA when combined with a strong immunogen induces an anti-CEA response for tumor therapy. Recent advances in recombinant vaccinia virus technology has permitted the development of recombinant CEA-vaccinia constructs that are being tested in a Phase I clinical trial initiated at the NCI in May 1993. Accrual to this trial, which is open to patients with adenocarcinoma of the gastrointestinal tract, breast, or lung, has been brisk. Fifteen patients have been enrolled, completing the second dose level of this trial. While no efficacy data is available at this point, there have been no significant hematologic or organ function toxicities to date.

Advances in Gene Therapy - Intramural and Extramural Research

Initial advances in gene therapy are being extended through pioneering clinical trials to determine if bone marrow precursor cells can be protected from the toxic effects of chemotherapy by selectively transferring the MDR (multi-drug-resistance) gene into these cells. A pilot study, run in collaboration with the NHLBI's Clinical Hematology Branch and the Clinical Center's Department of Transfusion Medicine, is now exploring the transfer and expression of the gene coding for resistance to the antibiotic neomycin that has been transferred into the bone marrow stem cells of breast cancer patients who are undergoing high dose chemotherapy and autologous bone marrow transplantation. Future plans call for similar experiments with the MDR gene.

Another innovative approach has been the use of "suicide vectors" to treat patients with the progressive or refractory brain cancer glioblastoma. Patients were treated with a retrovirus vector containing a gene which is taken up by the dividing malignant cells but not by normal brain tissue. The gene sensitizes cells to the drug gancyclovir. In the adult trial, five of eight patients treated with gancyclovir following this treatment showed a response. Based on these results, a pediatric trial has been initiated.

Advances in Diagnostic Imaging

NCI has the primary responsibility within the NIH for support of research in diagnostic imaging, both for development of new imaging technologies and support of the clinical trials necessary for evaluation of these technologies. Technologic advances in the capability for non-invasive detection of cancer have resulted in major improvements in the early diagnosis of breast cancer and in the determination of the extent of disease following initial diagnosis of many other types of cancer.

Extramural:

Digital mammography is the direct digital acquisition of x-ray shadows. These images can be stored, transmitted digitally and computer-enhanced to improve image quality. Digital mammography is being supported by the NCI Digital Mammography Development Group through grants to industry and academic radiology researchers. In FY 1994, NCI and NASA jointly issued a Program Announcement for grant applications for technology transfer imaging technologies developed for space and military purposes toward the reapplication for digital mammography.

Magnetic resonance breast imaging is capable of detecting breast cancers significantly smaller than those that can be detected with mammography. NCI will issue an RFA in FY 1994 for the clinical evaluation of MRI as a breast cancer detection tool.

Intramural:

Electron spin resonance (ESR) is a toll capable of detecting unpaired electrons or free radicals in either biological or non-biological aqueous systems. Newly available technology has allowed the development of extremely sensitive detector systems capable of detecting free radicals in very low concentrations. Because free radicals are more prevalent in malignant cells or inflammatory cells, as well as in injured cells such as the heart muscle cells following a myocardial infarction, the ESR imaging system could be important not only as a research tool for the study of cancer, inflammatory diseases, or cardiology, but could be a very sensitive clinical tool for early detection of cancer or other medical applications.

Positron emission tomography (PET) is an imaging technology capable of measuring the metabolic fate within cells of certain biochemical precursors, particularly glucose and amino acids. Because cancer cell have different metabolic capabilities from normal cells, PET is capable of detecting cancer cells with great specificity. PET has shown to be specific, although not highly sensitive, in detecting breast cancer in the lymph nodes of women diagnosed with breast cancer and is currently being developed as a detection method for breast cancer.

Rehabilitation Research - Extramural Research

The over 6 million cancer survivors in the United States include a sizable number whose lives have been substantially changed by their cancers or its treatment. Functional deficits and disability still occur, despite major advances in conservation surgery, organ-sparing procedures, and reconstruction. Besides cancer survivors, there are a large number of cancer patients currently undergoing treatment. NCI-sponsored rehabilitation research seeks to address the effects of cancer and its treatment in the context of enabling individuals to live as fully and effectively as possible within the limitations imposed by the disease or it treatment. It addresses the psychosocial and vocational components of individuals' lives, the physical factors as well as practical aspects of health care delivery.

The effects of cancer treatment on multiple organ systems and their impact on the individual's quality of life are critical issues. Extramural support for limb-sparing surgery for bone and soft tissue tumors, procedures to preserve speech and swallowing function in cancers of the head and neck, as well as multimodality approaches to breast conservation in early breast cancer has led to treatment advances which improve the cancer patient's long-term well being. Interventions are being developed and tested to facilitate the rehabilitation and re-entry of adult cancer survivors into society, as well as research of counseling programs and their impact on quality of life.

Intramural Research:

The importance of pain and symptom management to overall quality of life has emerged as a major health care issue. NCI initiatives are addressing improvements in assessing cancer pain; management of cancer pain outside of the acute care setting; diffusion of cancer pain knowledge and management into practice; and the special issues of cancer pain in children.

CANCER BIOLOGY

Research in cancer biology is supported through investigator-initiated projects that address a wide spectrum of topics and attempt to understand the details of how cancer grows and spreads. Information derived from these studies will identify new molecular targets which can be used for diagnosis, to create new methods of monitoring cancer, and new therapeutic strategies to either kill the cancer or to stimulate the immunity of the host to limit cancer growth.

Rationale for the Budget Request

The FY 1995 request of $309,839,000 represents an increase of $10,768,000 from the FY 1994 estimate. Efforts are supported through an Intramural Research program conducted by Federal scientists integrated with an comprehensive Extramural Research effort conducted by NCI grantees and contractors. The program plans for FY 1995 are as follows:

Tumor Immunology and Cancer Vaccines - Intramural and Extramural Research

Considerable progress has been made within the past year in vaccine efforts for non-viral cancers. The focus has shifted from establishing the existence of tumor antigens, to purifying them and cloning their genes, to determining how they can be used most effectively in vaccines. The advent of isolated, defined tumor antigens will facilitate studies on the mechanism of response to vaccines and permit more rapid development and testing of new vaccine candidates.

Progress has been made in the development of the mutated oncogenes ras and p53 as vaccine targets. Mutant p53 and ras genes produce tumor-specific oncoproteins that generate targeted cytotoxic T lymphocytes. Discrete peptide fragments of these mutant oncoproteins, when carried to the cell surface in association with major histocompatibility (MHC) class I molecules, can be targets for the cellular immune response -- a phenomenon known as "peptide immunization." The p53 peptide mutations are often quite specific for an individual tumor. Investigators have now developed the technology to isolate and rapidly synthesize tumor-specific immunogenic oncopeptides, using the patient's own mutation to prepare an autologous peptide vaccine that is selectively targeted to tumor cells containing the mutant gene product. Human clinical trials are scheduled for initiation shortly.

Intramural Research:

A new generation of tumor antigens holds exceptional promise. Several have been characterized and are being readied for clinical studies. This progress has been aided by advances in our understanding how T lymphocytes recognize tumor antigens. Tumor-associated antigens (TAA) may be useful vaccine targets. TAA are normal molecules expressed inappropriately or in unusually large amounts by tumor cells. Although also expressed on some normal cells, it has now been shown that vigorous anti-TAA immune responses can be induced in many cases without harm to the patient. As a first attempt at vaccine therapy directed against TAA, clinical trials have been initiated with carcinoembryonic antigen (CEA), which is expressed in some breast, colorectal, and other tumors. Also under development is a recombinant vaccine targeting human prostate-specific antigen (PSA).

Extramural Research:

Rapid progress has been made in using the secreted mediators of immune function known as cytokines to increase the response to cancer vaccines and in understanding what kind of response is most effective. Two distinct cytokine secretion and response patterns of helper T cells have been identified and it has been shown that the type of helper T-cell triggered is often the critical determinant of how effective an antitumor immune response will be. This is leading to a more focused study of cytokine effects *in vivo*. The idea of stimulating antitumor T-cell responsiveness by augmenting the availability of an auxiliary activation signal called costimulation has been successfully demonstrated in relevant animal models. As a result, there are now realistic prospects for a new generation of cancer vaccines that can induce a strong immune response restricted to the most effective arm of the immune system. The NCI will continue to support this critical area of research.

Studies of normal and dysfunctional B cells have now shown that B cells make and respond to an array of cytokines and express a number of specific cell-surface and intracellular molecules that contribute to B-cell regulation and are abnormal in lymphomas. Several have been uncovered while searching for the basis of inherited human immunodeficiency diseases. NCI-supported scientists have shown that one such disease, X-linked hyper IgM syndrome, is due to a failure in T cell-B cell communication. Another immunodeficiency disease, X-linked agammaglobulinemia, has been shown to be due to mutation in a critical intracellular signalling molecule of B cells, known as BPK. These mutations greatly increase the risk for developing B-cell lymphoma.

The Loss of Gene Function in Cancer Progression - Extramural Research

Much progress has been made in identifying the genes whose expression play a role in cancer, particularly genes that suppress tumor growth, such as *RB* and *p53*. When the function of these suppressing genes is lost, along with the normal restraints on cell growth, a cancer may develop. Because the cancer cell utilizes a number of strategies to eliminate the activity of these genes, this may be an absolute requirement for malignant growth. Tumor suppressors are sometimes found in mutated forms or the gene and its protein are just eliminated from the cell. Recently, powerful binding proteins which inactivate the proteins have been identified. Great effort has been made to discover just how these suppressor proteins work in the cell. NCI will continue to encourage this research, since it may ultimately be possible to develop a therapeutic technique to restore this activity to cancer cells.

It was recently shown that the mechanism of inhibition of *p53* is through its effect on specific stages of the proliferation cycle which a cell uses to replicate. The p53 protein can sense when the cell's DNA has been damaged and acts to stop the cell cycle until DNA repair can be made. It does so by either activating or repressing the transcription of other proteins by binding to the DNA of those genes. Recently a new protein called Mdm2 was discovered with two roles in this process: p53 represses expression of the *mdm2* gene, but when it is expressed it can inhibit the activity of p53 protein. This re-emphasizes the many critical steps involved cell growth regulation.

A family of RB suppressor proteins also acts through regulatory points of the cell cycle. RB is called a pocket protein because it is usually associated with a number of other proteins in tight complexes. The ability of these protein complexes to shift under various influences of the cell dictates whether or not RB can have suppressing activity. When RB and the other proteins are bound up in these complexes, they are unable to induce the transcription of genes necessary for cell cycle progression. The physiological state of the cell is closely linked to the state of these complexes and the loss of RB and disruption of the complexes frees the cancer cell from normal control mechanisms.

The Cancer Cell Microenvironment - Extramural Research

Cancer cells spread both locally and distally to establish new colonies through a process called metastasis. Normal epithelial cells do not have this capability; they are firmly anchored by receptors to proteins in their surrounding matrix. These adhesive matrix molecules are embedded in a meshwork of insoluble proteins between and around the cells. In tumor cells, some adhesive properties are lost. This matrix is actually a complex environmental system that contains other types of cells which influence the behavior of cancer cells. Stroma cells may produce growth factors that promote proliferation or motility of the tumor cells or express enzymes that assist the tumor cells in breaking away from the primary tumor. Their influence appears to play an especially prominent role in tumorigenesis of breast and prostate. This may be related to their dependence for growth and differentiation on hormonal steroids. The effects of hormones are frequently mediated to epithelial cells through fat and stromal cells. To promote a broad spectrum of research efforts on stromal-epithelial interactions and cancer progression, NCI issued a Request for Applications in 1994.

Another requirement for metastasis is that there must be a new blood vessel supply to allow tumor cell colonies to grow in their new sites. The extracellular matrix also contains the endothelial cells and related cell types needed to develop these blood vessels. New information has been accumulated about the various factors that can induce the generation of a new vascular system. Some of these are produced by and have been purified from tumor cells. Another new observation is that tumors also induce angiogenesis by shutting off the production of inhibitors of growth of endothelial cells. The inhibitors are apparently circulating factors which can maintain broad control of angiogenesis in an animal, whereas the inducing factors are usually localized within the tissue and may or may not be available for inducing vessel growth. This very rapidly developing research area will continue to be actively supported by the NCI, since it offers an important new avenue of investigation for improved cancer treatment.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Resource Development

1995 Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. Title IV, Part A, Section 408(a)(1)(A) of the National Cancer Act.
1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
57	$214,392,000	56	$234,737,000	56	$242,651,000	---	+$7,914,000

PROGRAM ACTIVITY:	FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
Cancer centers support	18	$151,936,000	18	$162,944,000	---	+$11,008,000
Research manpower development........	34	64,107,000	34	67,010,000	---	+2,903,000
Construction.........	4	18,694,000	4	12,697,000	---	-5,997,000
Total...............	56	234,737,000	56	242,651,000	---	+7,914,000

MECHANISM:	FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Research center......						
Basic research.....	12	23,487,000	12	23,444,000	---	-$430,000
Clinical/ comprehensive.....	42	100,344,000	44	106,961,000	+2	+6,617,000
Subtotal, centers	54	123,831,000	56	130,405,000	+2	+6,574,000
SPOREs............	23	26,816,000	26	31,232,000	+3	+4,416,000
Subtotal, centers & SPOREs...........	77	150,647,000	82	161,637,000	+5	+10,990,000
Other Research:						
Research career program............	171	14,386,000	171	15,201,000	---	+815,000
Cancer education.....	73	7,904,000	80	8,904,000	+7	+1,000,000
Total,Research grants	321	172,937,000	333	185,742,000	+12	+12,805,000
Training:	FTTPs		FTTPs		FTTPs	
Individual.........	163	4,323,000	163	4,444,000	---	+121,000
Institutional......	1225	33,168,000	1225	34,097,000	---	+929,000
Total, training....	1388	37,491,000	1388	38,541,000	---	+1,050,000
Research management.. and support........		5,810,000		5,868,000		+58,000
Construction.........		18,499,000		12,500,000		-5,999,000
Total, NCI.........		234,737,000		242,651,000		+7,914,000

Funding for the Resource Development budget activity during the last five years has been:

	Amount	FTE
FY 1990..............	168,297,000	46
FY 1991..............	170,595,000	49
FY 1992..............	218,101,000	58
FY 1993..............	214,392,000	57
FY 1994..............	234,737,000	56

Resource Development

CANCER CENTERS SUPPORT

The Cancer Centers budget supports two distinct programs: traditional cancer centers supported through Cancer Center Support Grants (P30), and the Specialized Programs of Research Excellence (SPOREs) supported through the P50 grant mechanism.

Traditional Cancer Center Support Grants (P30s)

The Cancer Centers Program supports 54 NCI-designated cancer centers -- basic, clinical, comprehensive and consortium -- through the Cancer Center Support Grant (CCSG) using the P30 mechanism. The CCSG provides the basis for creating a focus of cancer research within a university or research organization through an interactive environment, allowing investigators to convene, share ideas, explore innovative approaches to cancer, engage in collaborative research projects, and effectively translate laboratory findings into medical application. Cancer centers can take advantage of research opportunities to quickly and efficiently translate basic and clinical research findings into medical application and to maximize the best possible opportunity for every patient to achieve a cure. Although the CCSG provides a stabilizing framework for the operation of the Cancer Center, the majority of research support is provided by other grants and contracts making the overall success of cancer centers highly dependent upon the ability of scientists within the center to obtain research support. Many of the activities that characterize a cancer center, such as care, service and outreach, are not funded through the CCSG. The acquisition of substantial funds from other sources in support of these activities represents the significant economic leverage that results from the recognition and visibility that an institution acquires through being designated as an NCI cancer center. The Cancer Centers Program also supports cancer center planning grants (P20s) that allow smaller institutions three years to develop into a cancer center capable of applying for a CCSG. The aim of the planning grant initiative is to encourage the establishment of cancer centers in geographically underrepresented areas.

Specialized Programs of Research Excellence (SPORE)

The SPORE program was initiated in 1992 to accelerate translational research in the major cancer sites. Translational research applies basic laboratory findings to patients and populations, and conversely, applies clinical research findings to new laboratory studies that may lead to new hypothesis-driven clinical trials and interventions. The goal is to accelerate research advances to reduce incidence and mortality from these cancers, and improve patient survival and quality of life. SPORE grants are awarded to institutions that assemble teams of laboratory and clinical scientists dedicated to research involving a particular cancer site. The SPORE also maintains specialized research resources which include a human tissue procurement facility for investigative purposes. It provides opportunities for career development in translational research. A special feature of the SPORE is the developmental research program. This provides a significant and flexible source of funds to rapidly test novel ideas, and to respond to new research opportunities in a timely manner.

To date, nine SPORE (P50) awards have been made, four in breast cancer, two each in prostate cancer and in lung cancer, and one in colorectal and pancreatic cancer. The prostate cancer SPORE at the Baylor College of Medicine is designated the Matsunaga-Conte Prostate Cancer Research Center after Senator Spark Matsunaga and Congressman Silvio Conte. In addition, NCI has awarded 13 SPORE feasibility grants: five each for breast cancer and prostate cancer; two for lung cancer; and one for colorectal and pancreatic cancer. Feasibility awards permit institutions to further develop their SPORE capability and to participate in the SPORE network.

Rationale for the Budget Request

The FY 1995 budget request of $162,944,000 for Cancer Centers represents an increase of $11,008,000 over the FY 1994 estimate.

This request will support 56 CCSGs. The budget will provide continued support for noncompeting continuations and for the 17 CCSGs that are expected to submit competing renewals in FY 1995. In addition, 6 of the institutions currently holding P20 Planning Grants will compete for a new CCSG in FY 1995, along with a number of new CCSG applications from other institutions. Successful competition of institutions previously supported by the P20 planning grants would represent the maturation of this 3-year program which seeks to ensure the distribution of centers in geographically underrepresented areas.

In addition, the increase includes $4,000,000 for an RFA to stimulate the development of formal breast cancer research programs in NCI-designated cancer centers. Programs will engage in basic and clinical research approaches and will also explore opportunities for prevention and control research. Plans may include studies on breast cancer in elderly women or environmental factors and involve collaborations with the National Institute on Aging and the National Institute for Environmental Health Sciences.

New initiatives and enhancements have been planned for the Cancer Centers Program in FY 1995. These include plans to strengthen cancer prevention and control research; encourage research that addresses disproportionate cancer rates among women and minorities and other special populations; and stimulate research focused on high priority areas such as breast cancer, prostate cancer and AIDS-related cancers. Among the new allowances in the program is the provision in comprehensive cancer centers for an Associate Director for Community Research to identify research opportunities and resources through interaction with community leaders, physicians, state and local health organizations and tumor registries. A major responsibility will be to ensure that the research activities of the center address the cancers of highest incidence and mortality in their regions, as well as focus on the needs of minorities, special populations and other underserved populations.

Another new category in the CCSG guidelines is the provision for support of pilot projects and feasibility studies that provides cancer centers with an opportunity to explore new ideas and develop new projects to compete for independent funding through grants and contracts. It provides the NCI with a flexible instrument to target funds and specifically encourage projects focused on high priority areas such as breast cancer, prostate cancer, ovarian cancer, cervical cancer, gene therapy, vaccine development and AIDS-related cancers and cancer in the elderly. Pilot studies in the area of cancer prevention and control research will also be encouraged. The Cancer Centers Program plans to provide opportunities to enhance research in AIDS-related cancers; women's cancers, especially breast cancer; and cancer in the elderly. Because these areas of research complement ongoing efforts at other NIH-supported centers, the Cancer Centers Program will encourage these cross-cutting programs to take advantage of the research expertise found in centers supported by the National Institute of Allergy and Infectious Diseases, the National Institute on Aging, and the National Institute for Environmental Health Sciences.

Because the special issue of cancer among minority populations is a critically important, emphasis is placed on the need to address cancer in minorities throughout the multiple components of the Cancer Centers Program. For example, the Center's Associate Director for Community Research will assist in the development of new research approaches to disproportionate cancers among minority populations in the region. Cancer prevention and control research programs in cancer centers include research which focuses on cancer in minority populations. Finally, clinical research of the program directly or indirectly supported through the CCSG requires attention to the recruitment of minority patients to clinical trial protocols.

Included in the FY 1995 request is $31,232,000 for SPOREs, an increase of $4,416,000 over the 1994 estimate. This will permit continuation of the nine ongoing SPOREs, the thirteen existing SPORE feasibility programs, and four new awards for a total of 26 SPOREs. It will support the development of new initiatives within existing SPOREs and the development of innovative pilot studies for testing new ideas.

RESEARCH MANPOWER DEVELOPMENT

The Research Manpower Development programs are designed to recruit and develop well-trained independent investigators in the basic sciences and clinical disciplines who will become the nucleus of the cancer research effort for the next several decades. The overall goal is to train scientists who will be capable of pursuing independent research into the cause, prevention and control, detection and diagnosis, treatment, and rehabilitation of cancer.

Rationale for the Budget Request

The FY 1995 request of $67,010,000 represents an increase of $2,903,000 from the FY 1994 estimate. The program plans for FY 1995 are as follows:

National Research Service Awards (NRSA)

The NRSA program provides universities and research institutes with the opportunity to establish or enhance high-quality cancer research training environments and to provide stable, long-term basic or applied research training for predoctoral and postdoctoral trainees. The requested 1995 budget supports approximately 1,388 full-time training positions (FTTPs) for pre- and postdoctoral trainees funded through individual fellowships and institutional training grants at an increased stipend level consistent with NIH policy. This request maintains FTTPs at the 1994 level.

Research Career Program ("K" Program)

The Research Career Program provides the means and incentives for a commitment to an academic/research career. These awards permit young investigators to make a full-time commitment to research, which is essential for developing independent research skills and gaining experience in the basic sciences and clinical research. The requested budget will support current levels for the Clinical Investigator, Physician Scientist, Clinical Oncology Development, Preventive Oncology, and the Minority Health Professional Training Initiative awards.

Cancer Education Program

The 1995 request will continue support at current levels for the following cancer education objectives: collaborative programs to prepare predoctoral and postdoctoral students, medical practitioners, and behavioral scientists for careers in cancer prevention and control research and practice. The Program fosters the transfer of current knowledge and practice about the prevention, diagnosis, and treatment of cancer to community physicians, other health professionals, and minority populations; and provides training courses and workshops on cancer pain, rehabilitation, and psychosocial factors as well as student summer research assistantships. The NCI plans to use the Cancer Education Program to develop additional innovative education programs in cancer prevention, breast cancer, and minority health education initiatives.

CONSTRUCTION

The goal of the Construction Program is the creation of new and the modernization of existing facilities in order to meet the need for expanding cancer research at universities and medical centers throughout the nation. Grants are awarded to expand and upgrade the following types of facilities: basic research laboratories, clinical research facilities, research animal facilities, and a proton therapy facility. Construction funds are also used for building maintenance and repair at the Federally-owned Frederick Cancer Research and Development Center.

Rational for the Budget Request

The FY 1995 request of $12,697,000 represents a decrease of $5,997,000 from the FY 1994 estimate. The program plans for FY 1995 are as follows:

The FY 1995 request includes $7,500,000 for the continuation of Federal participation (on a 50:50 basis) in the construction of a new proton therapy center at the North-East Proton Center, Massachusetts General Hospital, Boston, Massachusetts. In addition, $5,000,000 is requested for the development of facilities to enable increased efforts to include breast cancer research studies and also for the maintenance and repair of facilities at the Frederick Cancer Research and Development Center in Frederick, Maryland. Upgrading of the facility is needed to comply with existing fire codes and biomedical laboratory safety regulations.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Cancer Prevention and Control

1995 Authorizing Legislation - Section 301 of the Public Health Service Act. Title IV, Part A, Section 408(a)(1)(A) and Section 408(a)(1)(B) of the National Cancer Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
231	$112,579,000	223	$153,809,000	223	$204,714,000	---	+$50,905,000

PROGRAM ACTIVITY:	FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
Cancer prevention and control........	223	$153,809,000	223	$204,714,000	---	+$50,905,000

MECHANISM:	FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Research management and support........		$8,550,000		$8,631,000		+$81,000
Cancer prevention and control:						
Inhouse..............	.	24,899,000		27,499,000		+2,600,000
Grants...............	117	48,296,000	200	78,037,000	+83	+29,741,000
Contracts............	206	72,064,000	251	90,547,000	+45	+18,483,000
Total, NCI...........		153,809,000		204,714,000		+50,905,000

Funding to the Cancer Prevention and Control budget activity during the last five years has been:

	Amount	FTE
FY 1990..............	80,524,000	186
FY 1991..............	90,798,000	198
FY 1992..............	114,913,000	225
FY 1993..............	112,579,000	231
FY 1994..............	153,809,000	223

CANCER PREVENTION AND CONTROL

NCI's cancer prevention and control research encompasses a full spectrum of basic through applied research, prevention clinical trials, and cancer surveillance. The translation of this knowledge into applications through technology transfer and health promotion activities for the public is a major Institute priority.

Rationale for the Budget Request

The FY 1995 request of $204,714,000 is an increase of $50,905,000 from the FY 1994 estimate. Cancer prevention and control research is predominately supported through a comprehensive Extramural Research effort conducted by NCI grantees and contractors, along with intramural research focused on nutrition and cancer prevention. The program plans for FY 1995 are as follows:

Chemoprevention Clinical Trials

Chemoprevention clinical trials are designed to develop safety and toxicity profiles of promising chemopreventive agents, define an agent's activity in selected patient populations and determine the usefulness of specific biochemical and biological markers to monitor drug efficacy and test qualified agents for their broad efficacy in large population studies. NCI's chemoprevention program is sponsoring trials to assess a highly diverse group of biological and chemical agents that have demonstrated anticarcinogenic activity. Approximately 23 agents are undergoing clinical testing, 400 agents are in preclinical testing, and over 2,000 agents are being tracked through the basic science literature. To speed and expand the identification of new chemopreventive agents, a variety of activities are in progress involving information processing, data analysis, and developing drug discovery groups to evaluate agents and combinations in preclinical and clinical testing.

Dietary Interventions

Diet and nutritional interventions combine chemoprevention and epidemiological research to test the role of diet in cancer prevention. Two studies were conducted in Linxian, China to determine if vitamin and mineral supplements would reduce cancers of the esophagus and gastric cardia in a high risk population. The results underscore the important role of nutrition in preventing cancer as well as other diseases. Diet and nutrient-dependent mechanisms in carcinogenesis and cancer prevention are also under intensive study. An understanding of these mechanisms may contribute to the design of dietary intervention trials for cancer prevention.

NCI's Interactive Research Project Grants support interdisciplinary collaborative research to address the complex questions about the role of diet and dietary components in cancer prevention. The relationship of dietary factors and major cancers, with particular attention on dietary fat and breast cancer, is also under investigation in a large-scale prospective study involving 3.5 million members of the American Association of Retired Persons in the initial screening, with the final cohort comprising 350,000 women and men aged 50-69.

The American Stop Smoking Intervention Study (ASSIST)

ASSIST is a collaborative effort between the NCI and the American Cancer Society, State and local health departments, and other voluntary organizations to develop comprehensive tobacco control programs in 17 states. Its purpose is to demonstrate that wide-spread, coordinated application of strategies to prevent and control tobacco use will accelerate the current downward trend in tobacco use. During the five year intervention phase, smoking control strategies adapted from science-based models will be implemented. Media, policy, and cessation support will be delivered to target groups using the health care system, schools, the worksite, and other community channels. As a result of these efforts, more than 4.5 million adults are expected to quit smoking and 2 million adolescents will be prevented from starting to smoke.

Minority Leadership Initiatives

Reducing cancer in minority and underserved populations is facilitated by mobilizing professional and lay community leaders to address specific cancer needs and by coalition building among health-related, academic and community organizations. NCI supports three such initiatives: the National Black Leadership Initiative on Cancer, the Hispanic Leadership Initiative on Cancer, and the Appalachia Leadership Initiative on Cancer to address the cancer prevention and control needs of these populations. NCI's "Model Cancer Control Delivery Systems" will develop, implement, and evaluate effective organizational models for making cancer prevention and control services more accessible to poor, minority and medically underserved populations by integrating these services into public health settings.

Native Americans

NCI is working with the Indian Health Service to address differences in cancer incidence, mortality and survival between minority populations and that of the general population. This project encourages consortia of existing cancer control-oriented research institutions and relevant regional health agencies to pool resources and address cancer control research projects in American Indian and Alaskan Native populations.

The Native American Women's Cancer Initiative was developed in response to the emerging cancer needs and issues of this population. Research goals emphasize the identification of barriers to culturally appropriate cancer control services such as screening, follow-up, diagnostic, treatment and rehabilitation programs for cancers common in or disproportionately elevated among Native American women. Other efforts seek to reduce cancer risk behaviors in these populations.

Education Efforts for Native Hawaiians and Samoans

NCI is encouraging developmental research in Native Pacific populations to assess their cancer prevention, early detection and treatment needs. A Request for Applications was re-released in 1993 for research to identify barriers to cancer prevention and control in Native Pacific populations. This initiative tests ways in which existing intervention methods can be used or adapted or new methods may be designed which are culturally sensitive to Native Pacific populations, thereby increasing their effectiveness.

Of all U.S. ethnic groups, Native Hawaiian women have the highest rates of breast cancer incidence and mortality. Yet these women vastly underuse the technology of mammography. For this reason, NCI is supporting outreach activities in the State of Hawaii to reach Native women with information about mammography and cancer early detection. NCI's Cancer Information Service (CIS) has a regional office in Hawaii which has developed plans for community outreach activities focused on mass media outlets and organizations that serve Native Hawaiians. These activities should increase understanding of the unique personal and cultural characteristics of Native Hawaiians that affect their use of cancer early detection techniques, and improve available materials and message appeals to reach and influence this population.

Native Hawaiian and American Samoan Cancer Control Research Network focuses on the unique cancer needs of these populations. The network encompasses a variety of collaborative efforts with Papa Ola Lokahi (the Native Hawaiian Board of Health established by the Native Hawaiian Health Care Act of 1988), the Office of Hawaiian Affairs, the Cancer Center of Hawaii, Native Hawaiian health organizations, traditional healers, scientific and lay community leaders, and civic leaders. NCI has also taken steps to encourage participation by Native Hawaiians and other underserved populations in clinical trials to ensure that the best possible health care is made available to them. NCI supports a planning grant at the University of Hawaii for the prevention and control of cancer in Hawaii and the mid-Pacific region and the development of culturally appropriate research and education for Native Hawaiians. NCI's toll-free information line (1-800-FOR-CANCER) has a regional office serving Hawaii where trained information specialists can provide callers with up-to-the-minute information about current clinical trials in which eligible patients may enroll.

National 5-A-Day Program

The National 5-A-Day Program, designed to encourage Americans to eat five or more servings of fruits and vegetables every day, represents a significant public/private enterprise between NCI and the Produce for Better Health Foundation. Research grants awarded to State health agencies, universities, and cancer centers are evaluating the effect of 5-A-Day activities in schools, workplaces and other community settings. State health agencies are working with industry to promote the program's messages.

National DES Educational Program

An NCI-sponsored initiative is providing information and recommendations to women exposed to diethylstilbestrol (DES), their families, and health care professionals. DES, a synthetic estrogen, was prescribed to pregnant women in the U.S. from 1945 through the early 1970s to prevent miscarriages and other pregnancy complications. Physicians and other health care professionals will be informed of the risks faced by patients exposed to DES and to their children. Standards for treatment will be developed and widely disseminated.

Cancer Control Activities in Cancer Centers

NCI is committed to strengthening and expanding cancer control and prevention activities at NCI-designated cancer centers. NCI will encourage the development of novel pilot projects for prevention and control, and will work with the centers to promote the development of a stable base of prevention and control researchers. Education grants will impact on academic curriculum and the development of more effective means for moving state-of-the-art knowledge into community settings.

Community Clinical Oncology Program

The Community Clinical Oncology Program (CCOP) is a network of cancer specialists, primary care physicians, and other health professionals who conduct both clinical treatment research and cancer prevention and control research studies. Primary objectives are the development of clinical trials to effectively implement cancer prevention and control research in multi-institutional settings for early detection and screening, chemoprevention, smoking, patient management, and rehabilitation. The current program involves 49 CCOPs and includes over 300 hospitals and 2,800 physicians. Development of cancer prevention and control research in the CCOP network has been increasing steadily since 1987, with approximately 4,000 patients enrolled annually in these studies. Several large-scale chemoprevention trials are being implemented through this network. The Minority-Based Community Clinical Oncology Program (MBCCOP), initiated to provide minority cancer patients with access to state-of-the-art cancer treatment and control technology, consists of eight programs involving 31 hospitals and 300 physicians with greater than fifty percent of new cancer patients from minority populations. MBCCOP patient accrual has grown to 10 percent of all ethnic minorities enrolled in NCI-approved clinical trials.

Breast Cancer Action Plan

The Secretary's Breast Cancer Action Plan calls for a wide range of activities designed to launch a multi-faceted approach against breast cancer. The NCI will work in cooperation with the Centers for Disease Control and Prevention and other agencies of the Department in order to address these goals to ensure that the most comprehensive approach for breast cancer research and outreach activities is pursued.

Breast Cancer Prevention Trial

The Breast Cancer Prevention Trial (BCPT) is underway in the CCOP clinical trials network. The BCPT tests the ability of tamoxifen, an anti-estrogen medication used in postsurgical treatment of early stage breast cancer, to prevent breast cancer development in women who are at increased risk for developing the disease. Approximately 16,000 women at increased risk for breast cancer due to age, family history, and personal history (i.e., age at first birth, age at menarche, and previous breast biopsies) are being randomized to receive tamoxifen or a placebo for an initial period of five years. The ten year study is being implemented in over 250 nucleus and sub-centers across the country and in Canada. Samples from trial participants will be analyzed for inherent genetic factors that may contribute to increased breast cancer risk.

Prostate Cancer Prevention Trial

A Prostate Cancer Prevention Trial using finasteride (Proscar) was initiated in FY 1993 in the CCOP clinical trials network. As prostate cancer is influenced by androgens, the study tests the ability of finasteride, which inhibits androgen synthesis, to reduce the incidence of prostate cancer. Because finasteride blocks the production of the hormone dihydrotestosterone, the trial will also focus on whether the long-term prophylactic use of the drug prevents the occurrence of benign prostate hyperplasia. The trial will involve 15,000-20,000 men at risk for prostate cancer. Subjects are being randomized to receive finasteride or placebo for up to ten years. The study's endpoint will be diagnosis of clinically significant prostate cancer.

Screening for Prostate, Lung, Colorectal, and Ovarian Cancers (PLCO)

The PLCO is a 16-year randomized trial in which 37,000 men will be screened for prostate, lung, and colorectal cancers and 37,000 women will be screened for lung, colorectal, and ovarian cancers. Patient accrual began in 1993, with equal numbers of men and women being followed with routine medical care as controls. There will be a 10-year follow-up of participants to determine the effects of screening on disease specific mortality. Diagnostic biopsy specimens will be examined to characterize any genetic alterations. The trial may allow the identification of biomarkers that will pinpoint cancers in their earliest stages.

Behavioral and Psychosocial Research

The quality of life for cancer patients can be improved through psychosocial and behavioral interventions designed to enhance the ability of patients and their families to cope with cancer. While psychosocial support is recognized as an integral component of cancer care, especially in the context of survivorship, a number of complex issues regarding psychosocial measures and interventions have not been adequately evaluated.

NCI is supporting research efforts to test the efficacy of counseling interventions to improve the quality of life in newly diagnosed cancer patients and in persons at increased risk of cancer. This initiative also addresses the impact of psychosocial counseling on survival by measuring physiologic parameters such as immune system response, which may affect the response to treatment and/or long term survival. A second research initiative supports the development, standardization, and pilot testing of methods to assess quality of life among cancer patients from diverse sociocultural backgrounds and will increase the use of standardized methods to assess their needs.

For American women ages 15-44 years, cancer is the leading cause of death. Despite their increasing survival, breast cancer remains the most common cause of cancer mortality for this age group. Issues facing young women diagnosed with breast cancer may differ from those of postmenopausal women. Diagnosis and treatment affect daily activities, such as the care of young children and other family responsibilities. A research initiative directed at problems confronting young breast cancer patients is in progress.

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The Surveillance Program

NCI's Surveillance Program monitors the U.S. cancer burden by measuring cancer incidence, mortality, and survival and assessing individual, societal, and health service factors that mediate these cancer measures. The major component is the Surveillance, Epidemiology, and End Results (SEER) Program, which consists of 11 population-based cancer registries covering 14 percent of nation's population. Because improving the nation's capability for measuring cancer rates and risks for minorities, the elderly, rural residents and the underserved is a major NCI priority, the SEER Program expanded in 1992 to include the nine million residents of the Los Angeles, California area. This increased national coverage to 25 percent of the U.S. Hispanic population, 41 percent of the Asian/Pacific Islanders, 17 percent of the American Indian population (mainly in the Southwest) and 12 percent of the African American population. Collaboration with the Bureau of the Census is improving the availability of regional population data to calculate cancer rates for minorities, particularly those residing in SEER areas.

As knowledge about the relationship between diet and cancer increases, the Surveillance Program is adapting its research activities in epidemiology and dietary assessment to measure trends in national dietary practices more comprehensively, enhancing dietary assessment methodology, disseminating nutrient analysis systems, and developing a portfolio of analytic investigations that provide guidance for cancer control programs. A dietary surveillance study has been initiated that is designed to provide improved baseline data for the Healthy People 2000 objective aimed at fruit and vegetable intakes. This research will lead to the development of new dietary assessment tools for epidemiologic research of diet and cancer, such as the prospective cohort study of diet and cancer in members of the American Association of Retired Persons (AARP) and the Prostate, Lung, Colorectal, Ovarian Cancer Screening (PLCO) Trial.

Understanding how screening, early detection, and cancer therapies are used by community physicians is of paramount importance. Linkage of databases from the SEER Program and Medicare claims files has produced an information and research resource for NCI and the Health Care Financing Administration (HCFA) in addressing these issues.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	419	385	374
Division of Cancer Etiology	557	515	500
Division of Cancer Biology, Diagnosis, and Centers	546	506	490
Division of Cancer Treatment	747	688	668
Division of Cancer Prevention and Control	213	196	193
Division of Extramural Activities	109	101	98
Frederick Cancer Research and Development Center	9	8	8
Total, NCI	2,601	2,400	2,331

	Average GS/GM Grade
1990	10.2
1991	10.3
1992	10.3
1993	10.4
1994	10.4
1995	10.3

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research, NIH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

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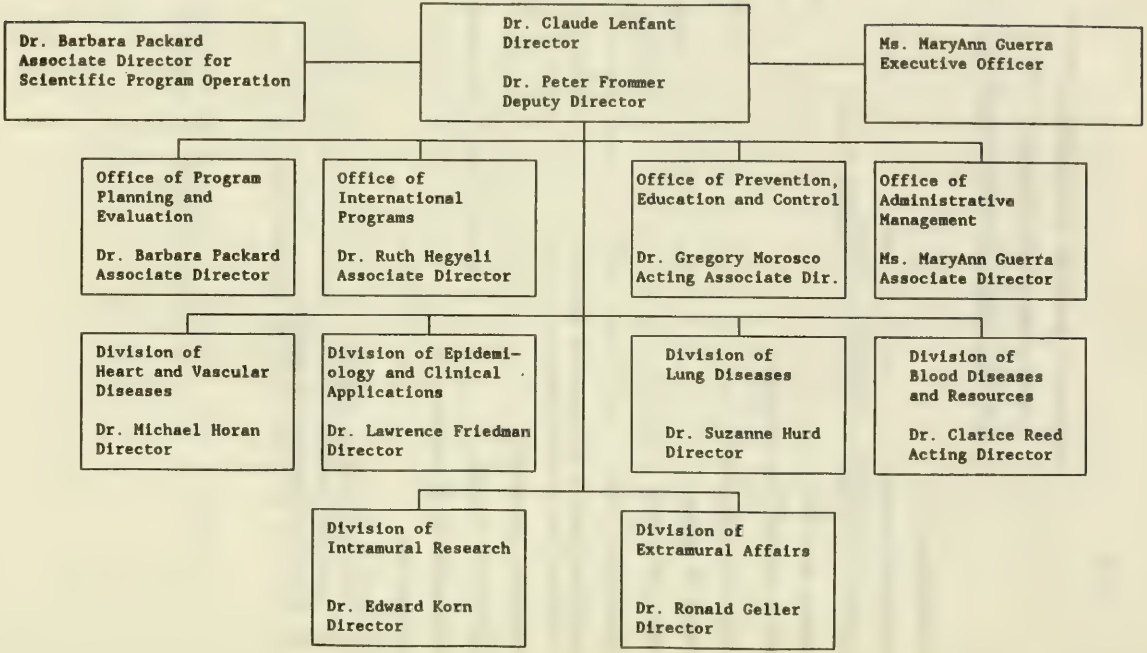
NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Heart, Lung and Blood Institute

For carrying out section 301 and 1105 and title IV of the Public Health Service Act with respect to cardiovascular, lung, and blood diseases, and blood and blood products, [$1,277,880,000] *$1,266,961,000 of which $13,870,000 shall not become available for obligation until September 19, 1995.* (Department of Health and Human Services Appropriations Act, 1994.)

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung and Blood Institute

Language Analysis

Language Provision	Explanation
"... of which $13,870,000 shall not become available for obligation until September 19, 1995."	This language ensures that government wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National, Heart, Lung, and Blood Institute

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$1,228,455,000	$1,277,880,000	$1,266,961,000
Section 511 .8% reduction	-9,827,000		
Section 513 consultant services reduction	-86,000		
Section 216 salary and expense reduction	-3,749,000		
Subtotal, adjusted appropriation	1,214,793,000	1,277,880,000	1,266,961,000
Real transfer to other accounts for Tuberculosis Research	-53,000		
Comparable transfer to Office of AIDS Research for HIV Activities	-48,058,000	-54,977,000	
Subtotal, adjusted budget authority	1,166,682,000	1,222,903,000	1,266,961,000
Unobligated balance, lapsing	-47,000	---	---
Total obligations	1,166,635,000	1,222,903,000	1,266,961,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1993 - $6,011,000; 1994 - $6,300,000; 1985 - $6,300,000.

Note: Excludes $420,269 for Royalties in FY 1993 and $252,000 in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting..........	2,037	$564,730,000	2,040	$590,468,000	1,857	$562,788,000
Admin. suppl..........	(153)	6,610,000	(105)	7,980,000	(105)	8,600,000
Competing						
Renewal.............	264	78,202,000	270	83,988,000	333	107,697,000
New.................	392	86,227,000	396	88,269,000	494	118,183,000
Supplemental........	4	601,000	4	655,000	5	828,000
Subtotal, competing...	660	165,030,000	670	172,912,000	832	226,708,000
Subtotal, res. proj..	2,697	736,370,000	2,710	771,360,000	2,689	798,096,000
Research Centers						
Spec./comp. ctrs......	68	94,261,000	73	101,630,000	73	105,807,000
Other research						
Res. career program...	348	28,818,000	365	30,200,000	365	32,303,000
Clinical Ed........	--	---	--	---	--	---
Coop. clin. research..	12	5,324,000	12	7,941,000	22	10,163,000
Bio. Res. Spt.........	--	---	--	---	--	---
Minority biom. res....		2,540,000		2,647,000		2,753,000
Other res. related....	67	8,229,000	84	9,059,000	84	9,313,000
Subtotal, other res.....	427	44,911,000	461	49,847,000	471	54,532,000
Total, research grants....	3,192	875,542,000	3,244	922,837,000	3,233	958,435,000

Training						
Individual awards:						
Noncompeting..........	109	3,200,000	97	2,955,000	136	4,382,000
Competing............	102	2,975,000	131	4,285,000	92	2,858,000
Subtotal, individual....	211	6,175,000	228	7,240,000	228	7,240,000
Institutional awards:						
Noncompeting..........	1,119	31,568,000	1,254	36,994,000	1,153	34,969,000
Competing............	227	6,533,000	108	4,011,000	209	6,036,000
Subtotal, institutional.	1,346	38,101,000	1,362	41,005,000	1,362	41,005,000
Total, training..........	1,557	44,276,000	1,590	48,245,000	1,590	48,245,000
Research & development contracts..............	149 FTEs	97,197,000	186 FTEs	98,210,000	202 FTEs	105,526,000
Intramural research.......	433	92,948,000	420	96,916,000	407	97,370,000
Research management and support............	478	56,719,000	465	56,695,000	452	57,385,000
Extramural construction...		---		---		---
Total....................	911	1,166,682,000	885	1,222,903,000	859	1,266,961,000
(Clinical Trials).........		(78,711,000)		(81,550,000)		(79,250,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Summary of Changes

1994 Estimated budget authority	$1,222,903,000
1995 Estimated budget authority	1,266,961,000
Net change	+44,058,000

	1994 Current Estimate Base		Change from base	
	FTEs	Amount	FTEs	Amount
Changes:				
A. Built-in:				
1. Intramural Research				
a. Within grade increase		$27,421,000		+$331,000
b. Annualization of January 1994 locality pay raise		27,421,000		+182,000
c. One less day of pay		27,421,000		-105,000
d. January 1995 pay increase		27,421,000		+328,000
e. Service and Supply fund increase		9,050,000		+218,000
f. Payment for centrally furnished services		36,244,000		+1,489,000
g. Increased cost of laboratory materials and other supplies		24,201,000		+786,000
h. FTS increase		135,000		+6,000
i. DHHS Working Capital fund		989,000		+7,000
Subtotal				+3,242,000
2. Research Management and Support				
a. Within grade increase		29,237,000		+409,000
b. Annualization of January 1994 locality pay raise		29,237,000		+201,000
c. One less day of pay		29,237,000		-112,000
d. January 1995 pay increase		29,237,000		+350,000

Summary of Changes--continued

e. Unemployment compensation and FECF.............	$236,000	+$35,000
f. Service and Supply fund increase........	3,600,000	+918,000
g. Payment for centrally furnished services...	10,406,000	+428,000
h. Increased cost of laboratory materials and other supplies...	6,321,000	+322,000
i. FTS increase...........	75,000	+7,000
Subtotal...........		+2,558,000
Total, Built-in..		+5,800,000

B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a. Noncompeting..........	2,040	598,448,000	-183	-27,060,000
b. Competing............	670	172,912,000	+162	+53,796,000
Total................	2,710	771,360,000	-21	+26,736,000
2. Research centers...........	73	101,630,000	--	+4,177,000
3. Research career program....	365	30,200,000	--	+2,103,000
4. Coop. Clinical research....	12	7,941,000	+10	+2,222,000
5. Minority biom. research....	0	2,647,000	--	+106,000
6. Other research related.....	84	9,059,000	--	+254,000
7. Individual training awards.	228	7,240,000	--	---
8. Institutional training awards..................	1,362	41,005,000	--	---
9. Research and development contracts................	186	98,210,000	+16	+7,316,000
	FTEs	Amount	FTEs	Amount
10. Intramural research........	420	96,916,000	-13	-2,788,000
11. Research management and and support.............	465	56,695,000	-13	-1,868,000
Subtotal.................				+38,258,000
Total changes..........				+44,058,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	885	859	-26
Full-time equivalent of overtime and holiday hours.......	4	4	---
Average SES salary..................	$110,805	$112,135	+1,330
Average GM/GS grade.................	10.00	9.97	-0.03
Average GM/GS salary................	41,970	42,350	+380
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)..................	70,322	70,322	---
Average salary of ungraded positions.........................	28,625	28,960	+335
Personnel compensation:			
Full-time permanent...............	$32,828,000	$32,786,000	-$42,000
Other than full-time permanent.....	8,043,000	7,997,000	-46,000
Other personnel compensation.......	1,998,000	1,986,000	-12,000
Special personnel service payments.	3,516,000	3,400,000	-116,000
Total personnel compensation.....	46,385,000	46,169,000	-216,000
Personnel benefits..................	10,259,000	10,213,000	-46,000
Benefits for former personnel........	34,000	34,000	---
Travel and transportation of persons.	1,143,000	1,137,000	-6,000
Transportation of things.............	271,000	267,000	-4,000

	1994 Appropriation	1995 Estimate	Increase or Decreas
Rent, communications, and utilities..	$2,376,000	$2,194,000	-$182,000
Printing and reproduction............	1,878,000	1,855,000	-23,000
Consulting services..................	1,975,000	1,960,000	-15,000
Other Services.......................	8,314,000	8,198,000	-116,000
Purchases from Govt. Accounts........	67,575,000	69,492,000	+1,917,000
Operation of GOCOs...................	---	---	---
R&D Contracts........................	92,218,000	99,136,000	+6,918,000
Supplies and materials...............	9,264,000	9,191,000	-73,000
Equipment............................	10,129,000	10,435,000	+306,000
Grants, subsidies, & contributions...	971,082,000	1,006,680,000	+35,598,000
Insurance claims and indemnities.....	---	---	---
Total budget authority by object...	1,222,903,000	1,266,961,000	+44,058,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NHLBI

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	32,828	32,828	32,786	(42)
11.3	Other than full-time permanent	8,043	8,043	7,997	(46)
11.5	Other personnel compensation	1,998	1,998	1,986	(12)
11.8	Special personnel services payments	3,516	3,516	3,400	(116)
11.9	Subtotal, personnel compensation	46,385	46,385	46,169	(216)
12.1	Civilian personnel benefits	10,259	10,259	10,213	(46)
13.0	Benefits for former personnel	34	34	34	0
	Subtotal Pay Costs	56,678	56,678	56,416	(262)
21.0	Travel and transportation of persons	1,449	1,143	1,137	(6)
22.0	Transportation of things	278	271	267	(4)
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	5,533	2,376	2,194	(182)
24.0	Printing and reproduction	1,544	1,878	1,855	(23)
25.0	Other Services	66,908	65,983	67,371	1,388
26.0	Supplies and materials	7,773	9,264	9,191	(73)
	Subtotal non-pay costs	83,485	80,915	82,015	1,100
	Total Administrative Costs	140,163	137,593	138,431	838

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1994 House Report	
Pediatric Cardiovascular Disease	
1. "Pediatric cardiovascular diseases are a significant source of morbidity and mortality in the U.S. Congenital heart disease, the most common type of birth defect, affects at least 8 of every 1,000 newborns. Congenital cardiovascular malformations account for 42 percent of all infant deaths due to congenital defects. The Committee encourages the continued support of research in pediatric cardiovascular diseases to reduce death and disability in children through the development of new prevention and treatment strategies." (page 53)	1. The NHLBI now supports pediatric cardiovascular centers at the University of Iowa, the Children's Hospital of Philadelphia, and the University of Rochester School of Medicine and Dentistry.
Gene Therapy	
2. "In establishing gene therapy centers the NHLBI recognized the potential of gene therapy for many genetically related diseases. Gene therapy seems especially exciting for the treatment of cystic fibrosis and certain cancers. NIH support has generated a critical mass of top scientists and institutes ready to develop this new technology, as seen in the response by researchers who submitted applications to NIH for the gene therapy centers initiated last year. To sustain the momentum needed to develop this new technology, the Committee has provided funds to expand these activities. This investment will enable scientists to pursue gene therapy research for cystic fibrosis and other genetic diseases." (page 54)	2. Six NHLBI-supported cystic fibrosis gene therapy centers are conducting research critical to achieving a cure for this devastating disease. Gene therapy research in cardiovascular and blood diseases includes new initiatives in sickle cell disease and hemophilias A and B. Other efforts focus on identification and mapping the genes responsible for hypertension, development of a mammalian genotyping service to identify the genetic determinants of cardiovascular diseases, and improved understanding of the molecular and cellular biology of hematopoietic stem cells for possible use as vehicles in gene therapy.

Item	Action Taken or to be Taken
Hemophilia	
3. "The Committee encourages NHLBI to fund an accelerated intramural and extramural scientific program in gene therapy and other promising areas of research aimed at seeking a cure for hemophilia." (page 54)	3. The NHLBI has initiated a new grant supported gene therapy research program for Hemophilias A and B. In addition, our intramural scientists are working to develop an adeno-associated viral vector, which contains the cDNAs of factors VIII and IX, the two blood coagulants missing in hemophilias, as a means of stimulating high and sustained levels of factor VIII and IX expression in the cells of hemophiliac patients. Success in these endeavors may result in effective and practical gene therapy for these patients.
Bionutrition	
4. "The Committee supports the research planned by NHLBI in the bionutrition area including new approaches to prevent cardiovascular, lung, and blood disease by improving nutritional habits emphasizing school settings and work sites. The Committee urges the Institute to continue its work in the bionutrition area, and has included funds for it to do so with a particular focus on women's health." (page 54)	4. The NHLBI supports clinical trials on antioxidants, which have potential to impede or retard atherosclerosis, including one on the primary prevention of cardiovascular disease and cancer in women. Other bionutrition studies are looking at dietary approaches to prevention and treatment of hypertension, and the effects of dietary factors on lipid metabolism, hypertension, clotting factors, and pulmonary status. Longitudinal studies are providing information on the effects of nutrition-related disorders over time, while demonstration and research projects in schools are evaluating the ability of various methodologies to influence smoking, nutrition, and physical activity as related to high cholesterol levels and high blood pressure. The NHLBI provides support for the Nutrition Coordinating Center at the University of Minnesota, and is preparing an Action Plan for Bionutrition Research.

Item	Action Taken or to be Taken
Transfusion Medicine	
5. "The Committee is aware that clinical applications of transfusion medicine are likely to yield health care cost reductions through disease prevention. Within the resources recommended by the Committee, the Institute will be able to continue its support of the transfusion medicine program, and other research initiatives that will improved the safety and efficacy of the nations's blood and tissue supply. The Committee is encouraged by reports of promising techniques that could make transfusion virtually disease-free, and is supportive of research directed to the most practical investments in this area." (page 55)	5. The objectives of the NHLBI Specialized Centers of Research program in Transfusion Biology and Medicine are to improve the safety and efficacy of blood and blood components, determine indications for their use, evaluate and possibly modify immunological responsiveness following their administration, and develop and evaluate alternative treatment strategies that substitute for certain of their functions or stimulate their endogenous production in order to reduce transfusion needs. A new program, In Vitro Inactivation of Viruses in Blood Components, focuses on basic and applied research to develop simple, cost-effective inactivation procedures to destroy the infectivity of transfusion-transmitted viruses in blood and blood components.
Sleep Disorders	
6. "Within the increase provided for the Institute, the Committee supports expanded research in the area of sleep disorders. The Committee has no objection to the establishment of a sleep disorders research center, as recently authorized, if the Institute believes it would be the best allocation of its resources." (page 55)	6. The NHLBI has taken the necessary administrative steps to establish the National Center on Sleep Disorders Research. One person has been detailed to the Office of the Director, NHLBI, to assist in the establishment of the Center, and office space has been allocated for it. An additional $4 million has been allocated for Center activities; the Center's first scientific initiative will focus on the cardiopulmonary consequences of sleep apnea.
Cooley's Anemia	
7. "NHLBI supports considerable work to ameliorate, and cure, Cooley's anemia and other anemias, and the Committee expresses its continued support of work in this	7. The Institute will continue a strong intramural research effort in Cooley's anemia, aplastic anemia, and similar disorders. Related to this research, molecular hematology

Item	Action Taken or to be Taken
area. The Committee also urges continued support of the Institute's molecular hematology initiative." (page 55)	is currently one of the most active program areas in the Institute. Several Institute-initiated grant programs related to molecular hematology will be funded in FY 1994. In addition, an important new centers program in stem cell biology is under development and will be announced shortly.

Item	Action Taken or to be Taken
1994 Senate Report	
Asthma	
1. "The Committee continues to be enthusiastic about the NHLBI Asthma Education Program and supports expanding the Childhood Asthma Management Program." (page 82)	1. The Institute continues to give high priority to this extremely important area.
Cooley's Anemia	
2. "Nearly a decade ago the Institute produced two widely used booklets on prevention through testing and understanding the diseases, and the Committee urges the Institute to work with the patient community to determine opportunities for updating those efforts." (page 83)	2. The NHLBI is considering how best to update the booklets, Cooley's Anemia: Prevention Through Testing and Cooley's Anemia: Prevention Through Understanding. The Institute currently distributes a leaflet on Thalassemia (Cooley's anemia) that was initially published approximately seven years ago.
Behavioral Cardiology SCOR	
3. "The Committee applauds NHLBI for its leadership in the behavioral sciences and urges NHLBI to redouble its efforts to elucidate the role of biobehavioral factors in the etiology, pathogenesis, and course of coronary heart disease." (page 83)	3. The NHLBI is considering new programs expected to have a substantial impact on progress in the area of health and behavior with respect to coronary heart disease. One of these focuses on biobehavioral mechanisms of essential hypertension in women and men under age 40 and would determine whether a systematic difference, by race or gender, exists in neuroendocrine and physiologic responses to psychosocial stress.

Item	Action Taken or to be Taken
	Another program would support research on enhancing recovery in coronary heart disease patients by determining the effects of psychosocial interventions on morbidity and mortality.
Transfusion Medicine	
4. "The Committee is encouraged by reports of promising techniques that could make transfusion virtually disease free, and it urges the identification and support of research directed to the most practical investments in this area." (page 83)	4. Same as number 5 in House Report
Molecular Hematology	
5. "The Committee encourages the Institute to expand its research programs in molecular hematology in disease areas most germane to its mission." (page 84)	5. Molecular hematology is leading the way in molecular medicine. New initiatives in gene therapy focus on finding cures for sickle cell disease and Hemophilias A and B; and developing methods to use hematopoietic stem cells as vehicles for gene therapy. Other research includes studies of cellular and molecular mechanisms responsible for blood abnormalities following HIV infection, regulation and development of megakaryocytes (cells that give rise to blood platelets) and control of platelet function, and the effect on graft-versus-host disease morbidity and mortality in patients given T cell-depleted marrow from unrelated donors. Specialized Centers of Research in Hemostatic and Thrombotic Diseases are planned to support basic research, facilitate transfer of basic knowledge to the bedside, and stimulate clinical studies in hemostatic and thrombotic diseases.

Item	Action Taken or to be Taken
Molecular Hematology	
6. "In addition, with an estimated 60,000 deaths per year from venous thrombosis, particularly as it impacts women, is an area of research the Committee encourages the NHLBI to pursue." (page 84)	6. Among its research activities in this area, the Institute will pursue a finding that may help identify more accurately patients that are prone to thrombosis. This research has high priority because a recent finding seems to indicate that a hereditary defect in plasma may provide clinicians with a more accurate method of identifying the population prone to thrombotic disease. If this finding is confirmed, clinicians could take measures to prevent deep vein thrombosis in patients at high risk.
Hemophilia	
7. "The Committee expects the Institute to maintain and expand this accelerated extramural research effort to the maximum extent possible in fiscal year 1994." (page 84)	7. The NHLBI has initiated a new gene therapy research program for Hemophilias A and B. An ongoing NHLBI intramural research project using retroviral vectors to express human factor VIII and IX, the two blood coagulation proteins missing in hemophiliacs, has successfully introduced genes that express small amounts of the needed proteins in cells grown in culture. Future plans include construction of an adeno-associated virus vector for factor VIII transfer and expression, in addition to continuing studies with the retroviral vector.
Bone Marrow Donor Program	
8. "The Committee is aware that the number of minorities, particularly African-Americans and Hispanics, on the donor roll of the National Bone Marrow Donor Program is not representative of their percentage of the U.S. population. Minority patients, therefore, are significantly less likely to find a suitable bone marrow donor than other Americans. The Committee is also concerned that minority patients have not, in the past, had sufficient access to transplant	8. Within the past year, the total number of potential donors in the registry has gone from 694,491 to 1,010,078, an increase of 45.4 percent. In the same period, minority donors increased from 99,512 to 167,232 (68.1 percent). The NHLBI supports seven subcontracts with the NMDP for minority recruitment: two each for Asians and Hispanics, and three for African-Americans. In May 1993, the NHLBI supported an NMDP-led training workshop on minority recruitment.

Item	Action Taken or to be Taken
centers. As noted in a recent GAO report, while progress has been made toward correcting this problem, more must be done. The Committee encourages and expects NHLBI to address the Committee's deep concern, to make this a priority and will contract with community-based, private, nonprofit organizations that have proven track record of recruiting minority donors." (page 84)	
Centers of Research in Pediatric Cardiovascular Disease	
9. "Congenital heart disease, the most common type of birth defect, effect at least 8 of every 1,000 newborns and accounts for 42 percent of all infant deaths due to congenital defects. The Committee recognizes that centers support innovative, multidisciplinary basic, and clinical research on congenital and acquired cardiovascular diseases in children and translate results rapidly to improvements in diagnosis, treatment, and prevention. With the additional funds appropriated for NHLBI, the Committee has provided sufficient funding to support three specialized centers of research in pediatric cardiovascular diseases to reduce death and disability from congenital and acquired cardiovascular diseases in children through the development of new prevention and treatment strategies." (page 82)	9. Same as number 1 in House Report
National Center for Sleep Disorders Research	
10. "Committee is pleased to learn the Institute is developing plans for the establishment of a National Center for Sleep Disorders Research within the NHLBI as authorized with the enactment of the National Institutes of Health Revitalization Act of 1993 and has provided additional funding for this new	10. Same as number 6 in House Report

Item	Action Taken or to be Taken
center. The Center will complement the sleep-related research currently undertaken by various NIH Institutes and will expand current activities in sleep research through a coordinated program of research, research training, and information dissemination relevant to sleep disorders." (page 84)	

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Authorizing Legislation

	PHS ACT/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation........	Section 301	42§241	Indefinite	>$1,174,658,000	Indefinite	>$1,218,716,000
National Heart, Lung, and Blood Institute..	Title IV, Parts B and C	42§284c	Indefinite		Indefinite	
National Research Service Awards.......	Section 487(d)	42§288	$400,000,000	48,245,000	Such sums as necessary	48,245,000
Total Budget Authority.				1,222,903,000		1,266,961,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Appropriations History

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$775,254,000	$853,088,000 2/	$863,652,000	$859,239,000
1986 Sequester				(36,947,000)
1987 3/	785,697,000	921,410,000	921,502,000	930,001,000
1988	821,887,000	990,808,000 4/	990,646,000	965,536,000
1989	1,015,471,000 5/	1,018,903,000	1,056,603,000	1,045,985,000
1990	1,039,846,000 6/	1,090,930,000	1,091,597,000	1,087,524,000 7/
1990 Sequester				(15,170,000)
1991	1,112,502,000	1,135,589,000 8/	1,137,235,000	1,126,942,000 9/
1991 Sequester				(15,000)
1992	1,209,924,000	1,202,398,000	1,190,396,000	1,188,593,000 10/
1993	1,245,396,000	1,228,455,000	1,228,455,000	1,214,793,000 11/
1994	1,198,402,000	1,277,880,000	1,277,880,000	1,277,880,000
1995	1,266,961,000 12/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes $40,206,000 in NRSA training programs and $3,300,000 in construction not considered.

3/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes, including $17,091,000 for NHLBI.

4/ Does not include funding for AIDS research consolidated at the Secretary's level.

5/ Excludes funds for AIDS research and education ($39,032,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ The 1990 request excludes funds for the National HIV program ($42,651,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

7/ Excludes enacted administrative reduction of $3,740,000.

8/ Excludes $44,476,000 in NRSA training programs not considered.

9/ Excludes Section 514 reductions of $31,708,000.

10/ Excludes Section 214 and 513 reductions of $9,398,000 and enacted rescission of $1,407,000.

11/ Excludes Section 215, 511, and 513 reductions of $13,662,000.

12/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTE	Amount
Extramural Research:												
Heart and vascular diseases program.......	--	$584,872	--	$613,439	--	$626,284	--	$658,103	--	$689,192	--	+$31,089
Lung diseases program....	--	182,089	--	192,861	--	205,738	--	213,386	--	219,539	--	+6,153
Blood diseases and resources program......	--	172,861	--	189,389	--	184,946	--	197,803	--	203,476	--	+5,673
Subtotal, extramural...	--	939,822	--	995,689	--	1,016,968	--	1,069,292	--	1,112,206	--	+42,914
Intramural research.......	429	88,091	445	91,295	433	92,948	420	96,916	407	97,370	-13	+454
Research management and support.............	471	51,596	486	56,880	478	56,719	465	56,695	452	57,385	-13	+690
Total, obligations.......	900	1,079,509	931	1,143,864	911	1,166,635	885	1,222,903	859	1,266,961	-26	+44,058
Unobligated balance, lapsing...............	--	50	--	23	--	47	--	---	--	---	--	---
Total, budget authority..	900	1,079,559	931	1,143,887	911	1,166,682	885	1,222,903	859	1,266,961	-26	+44,058

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTES are included in the NIH Office of AIDS Research.

Justification

National Heart, Lung, and Blood Institute

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
911	$1,166,682,000	885	$1,222,903,000	859	$1,266,961,000	-26	+$44,058,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Heart, Lung, and Blood Institute. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national research program to prevent, diagnose, treat, and cure heart, blood vessel, lung, and blood diseases; and to provide for an adequate and safe blood supply for the Nation. To achieve these goals, the Institute supports a comprehensive program of basic and clinical investigations, clinical trials, epidemiologic studies, and demonstration and education projects. This multifaceted approach has opened new and exciting avenues for biomedical research, and holds much promise for healthier and longer lives for the American public.

Current and Planned Programs

The Institute's current and planned programs are an investment in tomorrow's public health. The diverse research endeavors supported by the FY 1995 budget hold great promise for prevention and improved diagnosis and treatment of cardiovascular, lung, and blood diseases. For example, clinical trials are determining the safest, most efficacious, and cost effective treatments for several disease conditions. Other studies are assessing the effects of intervention programs to reduce risk factors for disease. In addition, modern molecular techniques are being used to explore the underpinnings of disease and develop genetic therapies leading to cure. The following are examples of several of these programs.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compares the incidence of major coronary heart disease events in hypertensive patients treated with diuretics to those receiving alternative antihypertensive drug treatments. In addition, the ALLHAT examines the relative effects of the treatments on cardiovascular mortality and morbidity, all-cause mortality, and quality of life. Findings from this study are expected to provide an important guide to physicians who treat hypertensive patients.

The collaborative molecular genetics initiative on asthmatics and their families plans to identify the major genes that lead to bronchial hyperresponsiveness, allergic sensitivity, and clinical asthma. New information generated by these studies is expected to elucidate the origins of asthma and lead to improved strategies for its prevention.

The Lung Health Study assesses the effect of a smoking intervention program and the use of an inhaled bronchodilating drug on the rate of lung function decline among men and women at high risk of developing chronic obstructive pulmonary disease. Study findings show gender differences in smoking cessation patterns, and have important implications for designing effective, gender-specific smoking cessation programs.

In utero gene therapy, accomplished by transplantation of stem cells containing a corrective gene, holds promise for new molecular approaches to cure genetic diseases such as sickle cell and Cooley's anemias. Recent progress in animal models indicates that stem cells can be transplanted into a pre-immune recipient fetus, without the need for tissue matching, marrow ablation, or immunosuppressive drugs; and without onset of graft-versus-host disease. If these findings can be successfully transferred to humans, genetic therapy using stem cells offers an alternative to bone marrow transplantation.

Research in molecular genetics offers unprecedented opportunities to define the mechanistic basis for such diseases as hypertension, stroke, sickle cell and Cooley's anemias, hemophilia, asthma, familial emphysema, and cystic fibrosis. Research in these areas will lead to early identification of individuals at risk for disease; and to improved diagnosis, prognosis, and treatment.

The NHLBI study on Postmenopausal Estrogen/Progestin Intervention assesses the effects of various hormone replacement strategies on risk factors for coronary heart disease, cancer, and osteoporosis in women. The study compares the effects of these strategies on a number of factors that affect risk of heart disease, including cholesterol and its fractions, blood pressure, fibrinogen, and insulin. Study results are expected to help establish a scientific basis for recommendations to women regarding hormone replacement therapy.

National Center for Sleep Disorders Research

The Institute has taken the necessary steps to create the National Center on Sleep Disorders Research, which is authorized by the NIH Revitalization Act of 1993. The functional statement and organization plan has been approved by the Director, NIH. The charter for the advisory board and nominees for membership have been submitted to the NIH. The Institute has also renovated space, has assigned one staff person to the Center, and is recruiting a second. The Center's first scientific initiative will focus on the cardiopulmony consequences of sleep apnea, and will examine possible associations between sleep apnea, and hypertension and stroke among different age, gender, and ethnic groups. The Institute has also initiated contact with all of the agencies listed in the authorizing legislation, and has discussed joint activities with some of them.

Community Health and Prevention

The Institute supports a broad range of prevention, demonstration and education, and other public and professional education programs in order to meet today's health challenges. In these programs, the Institute places special emphasis on meeting the needs of minority and other underserved populations. The following projects are illustrative of NHLBI's efforts in this area:

The Institute has made plans to add a passive smoking component to health education programs for new mothers. Previous Institute-supported studies that encouraged nonsmoking among new mothers showed a reduced prevalence of persistent lower respiratory symptoms in their babies.

A nutrition demonstration project is developing and validating nutrition education programs to reduce nutrition-related cardiovascular disease (CVD) risk factors in adults with low-literacy skills who are at risk for CVD.

Institute supported school-based cardiovascular risk reduction studies are investigating several risk factors (smoking, high blood pressure, and stress), as well as prevention-related activities--exercise and nutrition. These studies include substantial participation from racial and ethnic minority populations.

The Institute, in collaboration with the Department of Education, is currently pilot testing an "Asthma Awareness Curriculum for the Elementary Classroom." This curriculum is intended to be used with other health education information so that both teachers and students can learn more about asthma and asthma detection and treatment.

The President's appropriation request of $1,266,961,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Heart, Lung, and Blood Institute during the last five years has been as follows:

	Amount	FTEs
FY 1990	$1,028,641,000	864
FY 1991	1,079,559,000	900
FY 1992	1,143,887,000	931
FY 1993	1,166,682,000	911
FY 1994	1,222,903,000	885

Purpose and Method of Operation

The Institute organizes its research efforts around the major disease groupings for which it has responsibility. The Institute's Heart and Vascular Diseases Program, Lung Diseases Program, and Blood Diseases and Resources Program support research throughout the United States. The Institute also has a very active intramural research program in which Government scientists conduct important and cutting edge biomedical research of all types. All of these programs are supplemented by the activities of the Office of Prevention, Education, and Control; and the Office of International Programs. The NHLBI is also responsible for oversight of the National Marrow Donor Program.

All NIH components utilize similar mechanisms. Mechanisms utilized by the NHLBI include research project grants, specialized centers of research and comprehensive research centers, several types of research career awards, cooperative clinical research, demonstration and education research, research training, research contracts, and research conducted by NHLBI intramural scientists.

Overall Budget Policy

The FY 1995 budget request for the National Heart, Lung, and Blood Institute is $1,266,961,000, an increase of $44,058,000 over the the FY 1994 comparable appropriation level of $1,222,903,000.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The request includes $798,096,000 for 2,689 research project grants in FY 1995, compared to $771,360,000 for 2,710 grants supported in FY 1994. Within this total, 832 competing grants will be funded compared to 670 in FY 1994, an increase of 162 awards. The average cost of a research project grant increases by 5.6 percent, which exceeds the BRDPI. However, when AIDS-related grants are included the average cost is close to the 4.1 percent BRDPI increase. An increase is also included for administrative supplements for minority investigators.

At the request level, the Institute will continue to support 73 research centers, 365 research career awards, 84 other research related awards, and 1,590 individual and institutional full-time-training positions.

Additional funds are included for 10 new cooperative clinical research grants on genetic determinants of high blood pressure. An increase is also provided for minority biomedical research.

The request includes $105,526,000 for 202 research and development contracts, an increase of $7,316,000 and 16 additional contracts over the FY 1994 level.

In intramural research and research management and support, the request reflects the President's directive to reduce administrative costs and overall Federal employment. The FY 1995 budget includes funds for 859 full-time equivalent employees (FTEs) compared to 885 FTEs in FY 1994.

National Heart, Lung, and Blood Institute

EXTRAMURAL RESEARCH PROGRAM

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$1,017,015,000	$1,069,292,000	$1,112,206,000	+$42,914,000

This document provides justification for the FY 1995 Non-AIDS activities of the National Heart, Lung, and Blood Institute. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The major extramural programs, that is, those programs for which the Institute provides support but the research is actually conducted elsewhere, are the Heart and Vascular Diseases Program, the Lung Diseases Program, and the Blood Diseases and Resources Program. Extramural funding mechanisms utilized by the NHLBI include research projects grants, specialized centers of research and comprehensive research centers, several types of research career awards, cooperative clinical research, demonstration and education research, research training, and research contracts.

Funding for this program during the last five years has been as follows:

	Amount
FY 1990	$898,321,000
FY 1991	939,822,000
FY 1992	995,689,000
FY 1993	1,017,015,000
FY 1994	1,069,292,000

Rationale for the Budget Request

The FY 1995 budget request for the extramural research program is $1,112,206,000, an increase of $42,914,000 over the FY 1994 level of $1,069,292,000.

With the FY 1995 extramural request these funds will provide support for the following activities: Heart and Vascular Diseases Program, $689,192,000, an increase of $31,089,000 or 4.7% over the FY 1994 estimate of $658,103,000; Lung Diseases Program, $219,538,000, an increase of $6,152,000 or 2.9% over the FY 1994 estimate of $213,386,000; and Blood Diseases and Resources Program, $203,476,000, an increase of $5,673,000 or 2.9% over the FY 1994 estimate of $197,803,000.

Heart and Vascular Diseases

The Heart and Vascular Diseases Program seeks to continue progress against several of the Nation's most catastrophic diseases, including arteriosclerosis, coronary heart disease, cerebrovascular diseases, hypertension, and heart failure. Despite significant reductions in death rates over the last 20 years, coronary heart disease remains the number one cause of mortality in the United States, and cerebrovascular disease ranks number three. In the following material, the Institute is pleased to provide the latest information and describe the next steps in the continuing effort to further reduce the mortality and morbidity associated with heart and vascular diseases.

Coronary Heart Disease

Tissue-type plasminogen activator (tPA) is widely used to dissolve occlusive clots in coronary arteries of heart attack patients. It acts by breaking down the fibrin meshwork of the clot, thus dispersing the occlusion and allowing revascularization to occur. However, tPA also enters the circulation where it causes a significant depletion of circulating fibrinogen, an important component of the body's system for protection against hemorrhage. As a result of this undesirable side effect some patients have suffered severe bleeding complications after receiving tPA. Thus, molecular biologists have sought ways to modify the structure of the tPA molecule in a manner that would preserve the clot dissolving properties but prevent the systemic effect. This has been accomplished by altering the structure so that mutant tPA is inactive until it becomes attached to the fibrin in the occlusive clot. Another enzyme, plasmin then cleaves the tPA into an active form. This new drug may make it possible either to increase the dosage without risk of hemorrhage or to reduce the dose without compromising the rate of dissolution of the clot. If it becomes commercially available, it will improve the quality of care for the nearly 200,000 who receive thrombolytic therapy each year, and possibly extend this lifesaving treatment to a wider range of heart attack patients.

New research has documented the significant impact that depression may have on recovery from heart attack. Many previous studies have indicated that depression is common among heart attack survivors, and that patients with a high level of depression and psychological stress are significantly more likely than other patients to die of heart disease within five years of a heart attack. However, because most of this research relied on retrospective data, the findings have been subject to question. A recent prospective study found that patients who suffered a major clinical depression after a heart attack had a nearly six-fold increased risk of death within six months, even after history and severity of heart disease were taken into account. This is the first prospective study to demonstrate an independent impact of major depression on prognosis after a heart attack, and to establish that it occurs among women and among patients without significant arrhythmias. Whether treatment of depression would extend life in heart attack survivors is unknown, but constitutes an area for further investigation.

Hypertension

A new study, Dietary Approaches to Stop Hypertension (DASH), will provide important information about measures that can be used to prevent hypertension. About 50 million Americans currently have hypertension, and an additional large segment of the population has blood pressure in the range that, while not defined as hypertensive, still confers increased risk of mortality. Thus, hypertension prevention is a significant public health priority. Current recommendations of the National Blood Pressure Education Program Working Group Report on Primary Prevention of Hypertension emphasize lifestyle changes, particularly with respect to diet, that would be effective in the primary prevention of hypertension. Several dietary modifications (i.e., caloric restriction for weight loss and reduction in sodium and alcohol intake) have proven beneficial, but other promising approaches require investigation. DASH will test the ability of two dietary patterns--one high in fruits and vegetables, the other low in total and saturated fat and high in nonfat or low-fat dairy products--to lower blood pressure in individuals with high normal blood pressure or with mild hypertension. Two-thirds of study participants will be members of minority groups that suffer disproportionately from hypertension. Results from this trial are expected to provide additional dietary recommendations for use in public health and patient education aimed at both prevention and treatment of hypertension.

The NHLBI has initiated a large, long-term clinical trial, the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT), to determine whether or not treatment of hypertension with newer (and more expensive) antihypertensive drugs is superior to treatment with traditional drugs for prevention of fatal and nonfatal heart attacks. Hypertension, or high blood pressure, affects an estimated 50 million U.S. adults, and is causally implicated in the majority of strokes, as well as a large proportion of heart attacks and cases of kidney failure. Hypertension and its consequences affect black Americans disproportionately, so they will be particularly well represented in the study. Previous comparative drug trials have studied too few subjects for too short a time to uncover differences among drugs for major cardiovascular illnesses. Hence, this trial will include 40,000 subjects treated for an average of 6 years. The size of this study population will also allow the trial to address the question of mortality benefit of cholesterol reduction in older adults, using a subset of 20,000 trial participants. An innovative aspect of this study is its implementation through community practice settings rather than primarily academic centers to ensure cost-efficiency. This trial is expected to result in clear-cut recommendations either that newer drugs be used to treat hypertension because they exhibit superior effectiveness in heart attack prevention or, conversely, that conventional drugs be used because they are equally effective at considerably lower cost.

Modern molecular genetics has revolutionized medical research by providing powerful approaches to determine the location of genes that cause disease. Potential benefits include improved methods for pre-symptomatic diagnosis, carrier detection, primary prevention, and treatment. Recognizing the promise of this new field, the NHLBI has planned new, coordinated, and comprehensive programs to foster the application of molecular genetic approaches to hypertension. An Institute-wide program, The Mammalian Genotyping Service, is a shared support facility that will enable efficient, rapid genotyping needed to identify genetic determinants of complex diseases. Two other new programs will establish networks that focus on the role of specific genetic mechanisms in the development of hypertension. The Genetic Determinants of High Blood Pressure program will support collaborative investigators who share technology, data, skills, and biological materials as they delineate the major genetic factors of hypertension. Another program, Specialized Centers of Research on the Molecular Genetics of Hypertension will engage in mapping and identification of genes responsible for hypertension or its complications, pursue mechanistic studies on the biological consequences of variations in genes linked to hypertension or it complications, and encourage research utilizing molecular genetic techniques to elucidate basic mechanisms of normal and altered regulation of blood pressure. These efforts will enable the Institute to take full advantage of the exciting scientific opportunities in this rapidly emerging field.

Arrhythmias

A new clinical trial is expected to shed light on cost-effective treatment of serious arrhythmias, major causes of sudden death in the United States. The implantable cardiac defibrillator (ICD) has come into use as a means of treating sustained ventricular tachycardia (VT) and ventricular fibrillation (VF), both life-threatening arrhythmias. While the risk and cost --currently $80,000 per case--associated with ICD implantation may be reduced with the advent of newer systems that do not require major surgery, it is still unclear whether use of this device offers any survival advantage over more conventional antiarrhythmic drug therapy. The Antiarrhythmics versus Implantable Defibrillators (AVID) clinical trial will determine whether patients resuscitated from primary VF or sustained VT fare better with an ICD or with the drugs amiodarone or sotalol. These treatments will be compared with respect to cost and health quality of life, as well as mortality. A pilot study now under way will first establish the feasibility of conducting the full-scale trial. The findings from AVID will provide a valuable guide to management of patients with serious ventricular arrhythmias. By improving the ability to identify groups of patients likely to benefit from the ICD, the new information will facilitate appropriate use of this costly procedure.

Cerebrovascular Disease

Cerebrovascular disease remains a serious public health problem and the most common cause of neurologic disability in the United States. Recent results from basic research has led to identification of two distinct molecular sites within the brain that can contribute to brain damage after an experimentally induced stroke in animals. The work may have direct clinical applicability within a few years. One of these sites, the imidazoline receptor, binds a new antihypertensive drug known as rilmenidine, which can be protective against the devastating injury to the brain that often occurs with stroke. A second site, the N-methyl-D-aspartate receptor, can contribute to cell death in the brain following a stroke when it is excited by certain brain chemicals. Drugs that block the N-methyl-D-aspartate receptor can reduce the extent of brain damage. Moreover, molecular techniques that block the cell's production of the N-methyl-D-aspartate receptor are even more effective in reducing the extent of cell damage. Now that scientists are aware that both of these molecular sites are important mediators of the brain damage caused by stroke, they can focus on new clinical interventions to decrease the complications of the condition. These exciting developments may soon lead to new treatments to prevent the devastating complications of stroke.

Congenital Heart Disease

Congenital heart disease consists of a group of malformations of the heart that affect about 30,000 newborns in the United States each year. These malformations are the cause of cyanosis--"blue babies"--as well as severe heart problems requiring heart transplantation in childhood. For decades, research progress was slowed because it was thought that congenital heart disease was caused by a multitude of factors, both environmental and genetic. Recent advances in molecular biology have now established that many forms of this disease can be attributed to simple, identifiable, genetic defects. For instance, a study in dogs has found that a single chromosomal mutation is the cause of many types of human "blue baby" malformations. Other work appears to have identified a chromosomal mutation responsible for coarctation of the aorta, a common abnormality that causes heart failure and premature death if not corrected surgically. A third project has identified the gene responsible for supravalvular aortic stenosis, which can produce heart failure and other heart problems in infants and children. Increased research in this area of research is expected to provide new approaches for improved prenatal diagnosis and treatment, genetic counseling for disease prevention, and, perhaps ultimately, gene therapy for congenital heart disease.

Prevention Research

Because knowledge of the national serum total cholesterol levels is used to develop strategies for coronary heart disease (CHD) prevention, and to monitor the effectiveness of those strategies, the National Health and Nutrition Examination Survey (NHANES) periodically measures cholesterol levels on a nationally representative sample of the civilian, noninstitutionalized population of the United States. Data from the first phase (1988-1991) of NHANES III show that mean serum cholesterol levels in U.S. adults consistently declined from 1960 through 1991 in men and women of every age group. Levels fell by approximately 6 percent in men and 8 percent in women; over half of the decline occurred in the period 1976-1991. The proportion of adults with high blood cholesterol ($\geq$ 240 mg/dL) fell from 26 percent to 20 percent, while the proportion with desirable levels ($<$ 200 mg/dL) rose from 44 percent to 49 percent. These results suggest that the Healthy People 2000 goal of reducing the mean serum cholesterol level of U.S. adults to no more than 200 mg/dL is attainable. The cholesterol changes could account for a substantial proportion of the marked decline that has occurred in deaths from coronary heart disease and, in the long run, should have a favorable impact on the very high costs associated with coronary morbidity and mortality.

Hormone replacement therapy (HRT) is widely used among postmenopausal women, but its relationship to cardiovascular risk profiles remains uncertain. Reports from two large cohort studies, Atherosclerosis Risk in Communities (ARIC) and the Cardiovascular Health Study (CHS), recently demonstrated highly favorable cardiovascular disease risk profiles in users of HRT. Among 5,000 women aged 45-64 years in ARIC, postmenopausal women taking estrogen and progestin preparations had better blood lipid levels than women who used no hormones or used estrogen alone. These improvements included higher levels of HDL-cholesterol and lower levels of LDL-cholesterol and fibrinogen, a blood clotting factor. The more favorable risk factor profile in these women could potentially translate into about a 40 percent lower risk of developing coronary heart disease.

Lung Diseases

Pulmonary diseases are among the fastest rising causes of death and account for more bed days, work loss days, and physician office visits than any other major disease group. Chronic obstructive pulmonary disease (COPD) and allied conditions now rank fifth among the ten leading causes of death in the United States. Asthma-related hospitalizations and deaths are increasing, particularly among certain minority groups. The following material describes the Institute's progress and plans to reverse these unfavorable trends.

Cystic Fibrosis

Patients with cystic fibrosis (CF) vary widely in the severity of their disease as a result of mutations in a gene programmed to produce a protein that controls the flow of chloride in and out of cells. Improved understanding of this phenomenon now suggests new therapeutic approaches. Research has shown that patients with the most severe disease have mutations that fail to produce a protein, or produce a protein that is misfolded and, therefore, is not delivered to the cell membrane. On the other hand, mutations that permit movement of the protein to the cell membrane but result in its defective regulation or in reduced flow of chloride through the cell membrane cause milder disease. Using the recently developed CF animal model, researchers have discovered that expression of an "alternative" pathway in cells protects an organ from the ravages of an altered or missing protein. It is possible that the relative expression of this "alternative" chloride pathway also may contribute to the range of severity of pulmonary disease observed in CF patients. This observation provides the rationale for the use of chemicals called nucleotides in therapy of CF lung disease. By interacting with appropriate receptors on the surface of airway cells, these nucleotides trigger the movement of chloride from airway cells through this "alternative" chloride pathway. Preliminary studies have indicated that nucleotides cause no adverse effects and are effective in increasing the clearance of mucus from the airways. If confirmed in studies in CF patients, this may represent an innovative approach to alleviating the pulmonary complications of CF.

Asthma

Despite major advances in understanding the etiology and pathophysiology of asthma and development of new therapeutic approaches, the prevalence and severity of asthma, as well as its economic burden, have significantly increased over the past decade. To address this growing problem, the Institute recently established an Asthma Clinical Research Network consisting of five clinical centers and a data coordinating center. This interactive network has been organized to facilitate rapid evaluation of new therapeutic entities, assess current treatment strategies, and efficiently disseminate laboratory and clinical findings to the health care community. Each clinical group has the ability to access at least 400 patients with clearly defined and documented asthma, and the study population will encompass a broad range of age groups with appropriate gender and minority representation. Collaborative protocols implemented by the network will emphasize evaluation of investigational drugs, approved agents not currently used for the treatment of asthma, and optimization of conventional therapy, particularly in women, children, and the elderly. This program is intended to provide the infrastructure required for rapid completion of multiple therapeutic trials in a well-characterized population of patients with asthma and for timely communication of results to the medical community.

Chronic Obstructive Pulmonary Disease

Findings from basic research laboratories have shed new light on the pathogenesis of chronic obstructive pulmonary disease (COPD), now the fourth most common cause of death in the United States. For example, one of the key events in COPD is chronic inflammation and destruction of the air sacs where gas exchange takes place. This destruction is caused by enzymes released from white blood cells. Previously, it was thought that the damage was limited when the enzymes were inactivated upon forming complexes with inhibitors in tissue fluids. However, it has now been found that the enzyme complex itself increases inflammation by attracting more inflammatory cells. Related research has demonstrated that patients with an accelerated course of emphysema often have a genetic defect that causes a deficiency in the secretion of one of the main inhibitors of inflammatory enzymes, alpha$_1$-antitrypsin (AAT). The portion of AAT needed for secretion has now been identified and characterized. Meanwhile, development of gene therapy for AAT deficiency moved a step closer to clinical application, as trials in experimental animals resulted in stable production of AAT for one year. Each of these incremental improvements in our understanding of COPD or its therapy can lead to new ways to treat COPD patients or prevent people at risk from developing COPD.

Lung Cell Biology

Gene therapy has generally been conceived as principally applicable to potential treatment of diseases, such as cystic fibrosis, that result from an inherited genetic abnormality. However, a much larger group of diseases might be treatable by transiently engineering host cells to produce beneficial proteins. This new approach was tested by NHLBI-supported investigators who recently described a relatively noninvasive and nontoxic procedure that could allow the transient expression of proteins that are beneficial in alleviating lung injury. They found that a functioning foreign gene, encoding a physiologically relevant secreted human protein, can be introduced into lung endothelial cells in culture and into the lungs of intact animals, and that expression of the gene can be controlled. They also found that expression of the protein of interest was lost after a few days, a desirable property for a short-term therapeutic agent. Temporary increases in antioxidant enzymes or in growth factors that are potentially useful in lung repair, or other mediators important in regulating lung inflammation, might be particularly beneficial in treating acute lung injury. This new approach will permit elucidation of molecular mechanisms affecting gene expression in lung cells and specific investigation of the roles of various proteins in lung cell responses. In addition, the ability to engineer transient alterations in lung cell function could make gene therapy applicable to a broad range of lung diseases, including those not due primarily to inherited abnormalities.

Pulmonary Fibrosis

Pulmonary fibrosis is a potentially fatal disorder that may arise as a result of various assaults on the lung. It begins with a marked inflammatory phase that is thought to set the stage for the later fibrotic phase of the disease. This sequence has stimulated much work directed at understanding the role of molecules called cytokines that are produced during the inflammatory phase. To understand the molecular mechanisms involved in production of fibrosis by these cytokines, researchers are pursuing ways to define more precisely the distinct cytokine/target cell interactions that occur. Pulmonary immunologists recently combined use of strains of animals sensitive and resistant to fibrosis with a new technique to determine the level of a variety of cytokines in the lung during development of pulmonary fibrosis. They found one cytokine at increased levels in the lungs of sensitive animals and another at increased levels in resistant animals. Levels of a third cytokine appeared to be high in sensitive animals produced by crossbreeding sensitive and resistant animals, suggesting that it is involved in sensitivity to pulmonary fibrosis. Further studies to sort out which cells and cytokines determine susceptibility to fibrosis in this model are expected to provide important information on why some individuals tend to develop fibrosis while others do not. If the molecular basis for fibrogenesis can be determined, new approaches will become available to prevent the fibrosis associated with a wide variety of diseases that affect the lungs.

Tuberculosis

The unforeseen resurgence of tuberculosis (TB) as a U.S. public health problem has highlighted the importance of ensuring that health-care providers have up-to-date knowledge of how to diagnose, manage, and prevent TB. To help meet this need, the NHLBI has initiated a Tuberculosis Academic Award program to stimulate improvements in medical curricula related to TB and foster collaborative efforts between medical schools and community organizations to aid in TB control efforts. The six awards made in FY 1993 represent a variety of approaches. Modern TB control presents a complex challenge because of many factors, including difficulties associated with reaching homeless persons, migrants, and disenfranchised patients; coping with multiple-drug resistance to treatment; and enforcing patient compliance with long-term treatment regimens. The Tuberculosis Academic Award program is expected to make a major contribution toward solving this important public health problem.

Blood Diseases and Resources

The importance of blood in sustaining health and treating disease is unmistakable. Disorders of the blood such as thrombosis play a major role in the course of a variety of diseases, particularly cardiovascular diseases. Chronic blood diseases--sickle cell disease, Cooley's anemia, and hemophilia--require lifelong care and cause death in approximately 1,000 Americans each year. The maintenance of an adequate and safe blood supply is a major public health concern, accentuated by the rapid increase in the AIDS epidemic and the continuing threat from hepatitis. Finally, a new treatment frontier is opening, which features the increasing use of bone marrow transplantation and experiments in gene therapy that utilize marrow stem cells.

Bone Marrow Transplantation

Recent growth in the size and diversity of the National Marrow Donor Program (NMDP) registry of volunteers is reflected in improved prospects that patients needing a marrow transplant will receive it. Allogeneic bone marrow transplantation (from another, non-identical person) can be curative for a number of otherwise fatal blood and genetic diseases but many patients who are candidates for this treatment have no suitably matched relative to be the donor and, hence, must rely upon marrow from a carefully selected unrelated donor, matched for tissue-type. Within the past year, the total number of potential donors in the registry has grown from 694,491 (9-27-92) to 1,010,078 (10-3-93), an increase of 45.4 percent. In the same period, minority donors increased from 99,512 to 167,232 (68.1 percent). Formal, or "active," searches done on behalf of white patients now successfully lead to a transplant 40-42 percent of the time, increased from 33-35 percent in the past year. While the success rate for blacks and Hispanics remains lower, it has improved from 17-19 percent a year ago to 22-24 percent now. Evaluation of marrow donor tissue typing suggests that a 50-60 percent success in finding fully matched donors may be achievable, but a higher rate would require a prohibitively large marrow donor registry. Thus, researchers are vigorously pursuing alternative strategies.

Sickle Cell Disease

The Institute has initiated a new research program to explore genetic therapy approaches to cure sickle cell disease, a worldwide health problem of considerable magnitude. A number of recent advances have paved the way for rapid progress in this area. The molecular biology of hemoglobin gene regulation has supplied sufficient knowledge to achieve normal expression of hemoglobin genes introduced into red cell precursors, which may be manipulated outside the body and subsequently reintroduced into the patient. The recent development of adenoviral vectors offers an efficient means of achieving gene transfer in humans. Finally, new methods allow accurate and efficient isolation of red blood cell precursors from bone marrow, peripheral blood, and fetal umbilical cord blood. The cure of sickle cell disease by gene therapy would have a significant impact on the health of black Americans, and greatly reduce the cost of care for sickle cell disease, which exceeds $700 million annually. Moreover, techniques developed in the course of this research effort may have applicability to other hereditary hemoglobinopathies, such as Cooley's anemia.

Hemophilia

Hemophilia A is a hereditary bleeding disorder that results from a deficiency in blood coagulation protein factor VIII. Affected individuals are subject to spontaneous bleeding episodes and risk crippling joint injuries or life-threatening hemorrhage. The seriousness of the disorder is related to the level of factor VIII activity and is classified as severe, moderate, or mild. Sequencing of the factor VIII gene and subsequent studies identified mutations in most of the mild-to-moderate patients and approximately half of the severe patients. Recently, investigators described how a recombination of a DNA sequence could lead to an inversion and a disruption of the factor VIII gene. An assay, which requires only a blood sample, was developed and can be used for genetic prediction of hemophilia A in approximately half of the families with severe disease. This assay can also be used for prenatal detection, which may enable early and improved therapy for the young hemophiliac.

Thromboembolic Disorders

Some individuals have a known tendency to develop venous thromboembolic disease, but for the large majority of thrombotic patients, no reliable molecular abnormality has been reported that may be used to identify those prone to venous thrombosis. Indeed, an abnormality in plasma proteins has been established in only 20 percent of the population with thrombosis. A hereditary defect in the plasmas of three unrelated thrombotic patients who gave a poor anticoagulant response to a plasma enzyme known as activated protein C was recently reported. This defect has now been confirmed in 52-64 percent of a group of previously undiagnosed patients with a tendency toward thrombosis. If these results hold true in future studies, this line of inquiry may lead to development of new, sensitive tests for accurate identification of the population that is prone to thrombosis so that appropriate prevention measures may be taken. Such an advance would have significant public health implications, given that about 2 million Americans develop deep vein thrombosis and approximately 60,000 die of it annually.

Transfusion Medicine

Over the past two decades, advances in transplantation and transfusion science have resulted in powerful new therapies for kidney disease, heart disease, diabetes, and malignancies. Despite the progress made, the single biggest complication limiting therapy is still the rejection of the graft or the transfusion because the recipient's immune system becomes sensitized to, rather than tolerant of the mismatched donated tissue. A logical approach to resolve this problem would be to induce specific suppression or tolerance for the foreign transplantation antigens involved, without affecting host immune response to infections. During the past year, a model to induce nontoxic, specific tolerance to foreign transplantation antigens has shown promising preliminary results. This research will continue in FY 1995.

National Heart, Lung, and Blood Institute

INTRAMURAL RESEARCH

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
433	$92,948,000	420	$96,916,000	407	$97,370,000	-13	+$454,000

This document provides justification for the FY 1995 Non-AIDS activities of the National Heart, Lung, and Blood Institute. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The Intramural Research Program of the Institute conducts an exciting and diverse basic and clinical research program on diseases of the heart, blood vessels, lung, and blood in facilities at the National Institutes of Health. The Institute continues cutting edge research that has resulted in significant advances in gene therapy and bone marrow transplantation, and treatment of hemoglobin disorders. Orientation of the research program is moving toward macromolecular structure, cellular biology, molecular biology, genetics, and molecular medicine, including gene therapy. Noteworthy advances and our future plans are described in the material that follows.

Funding for this program during the last five years has been as follows:

	Amount	FTEs
FY 1990	$80,281,000	422
FY 1991	88,091,000	429
FY 1992	91,295,000	445
FY 1993	92,948,000	433
FY 1994	96,916,000	420

Rationale for the Budget Request

The FY 1995 budget request for the Intramural Research Program is $97,370,000, an increase of $454,000 from the FY 1994 level of $96,916,000.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease and the leading cause of sudden cardiac death in otherwise healthy young people. Mutation to the gene that produces a particular protein, the beta myosin heavy chain (BMHC), has been confirmed in some families with HCM. It has also been demonstrated that HCM is genetically heterogeneous, in that it has been found in no more than 30 percent of families linked to mutations in the BMHC gene. Thirteen distinct mutations have been identified in seventeen different kindreds. Each of the mutations is associated with different clinical manifestations and prognoses. Presently, investigators are attempting to identify HCM kindreds with distinct BMHC gene mutations so that they can improve risk stratification among their patients. A recent finding that mutations of the BMHC gene are expressed in skeletal muscle has allowed skeletal muscle to be used in exploring and characterizing functional BMHC defects in HCM. Additional large families are being studied to determine the genetic basis of HCM for the 70 percent of families not linked to the BMHC gene and to identify other possible mutations in the BMHC gene associated with HCM. Enhanced understanding of the underlying genetic basis for HCM will ultimately lead to improved diagnosis, and to treatment regimens tailored to the individual patient.

Intramural investigators also have demonstrated that dual chamber pacing is at least as effective as the available surgical approaches and offers several advantages in the treatment of HCM patients who have drug-refractory, left ventricle obstruction. As a result of this work, pacemakers optimally designed for HCM patients are likely to be developed that will offer further improvement in HCM therapy.

Gene Therapy

Researchers in the intramural laboratories of the NHLBI have continued to advance the frontiers of gene therapy. They previously demonstrated the potential for adenovirus to deliver the normal cystic fibrosis transmembrane regulator (CFTR) gene into airway epithelial cells, both *in vitro* in human cells and *in vivo* in an animal model. Although the first human study of gene therapy for CF was performed by NHLBI intramural investigators during the past year, a number of additional obstacles remain to be overcome before gene therapy is a reality.

While continuing to develop and refine gene therapy approaches to CF, investigators are also addressing another genetic disease that is a candidate for human gene therapy using an adenovirus vector. Individuals with alpha-1-antitrypsin (AAT) deficiency disease experience an accelerated course of emphysema. AAT is an antiproteases that is essential to protect the walls of the alveolar compartments from protease-mediated destruction. NHLBI investigators have demonstrated in an animal model both the feasibility of adenovirus-mediated gene transfer targeted to the peritoneal mesothelium, the membrane lining the abdominal wall and the subsequent synthesis and secretion of human AAT. Further study is needed to clarify the mechanisms involved before investigators can use the technique in patients with AAT deficiency.

Fanconi's anemia, another disease targeted for gene therapy, is an autosomal recessive disorder that produces aplastic anemia. Bone marrow transplantation, the only current curative therapy, is unsatisfactory in that it entails a significant risk of early mortality. Researchers have found the gene for Fanconi's anemia type C and have cloned it. The sequence for the gene has been incorporated into retrovirus and adenovirus vectors. The vectors have similar and marked effects on hematopoietic stem cells from patients, dramatically increasing colony formation. Protocols for the use of these vectors in patients are being developed that should ultimately lead to a life-saving approach to gene therapy for Fanconi's anemia.

Hemophilia is normally caused by a lack of Factor VIII or Factor IX. Present treatment consists of regular injections of the missing factor. Several new developments have contributed to the goal of treating hemophilia with gene therapy. Vectors have been constructed that express low levels of factor IX in T and B cell lines, primary lymphocytes, and enriched bone marrow hematopoietic stem cells. Also, a class of retroviral vectors was developed that contain spliced messenger RNA for factor VIII. The ultimate goal of this research, successful gene therapy, will provide adequate production of the missing factor VIII or IX and thereby eliminate the need for continued injections.

Heart Failure

Chronic heart failure affects between two and three million Americans and constitutes the leading cause of hospitalization among persons over 65 years of age. Understanding the fundamental differences in the processes underlying the contraction and relaxation of the normal and failing heart is essential for developing improved methods of treatment for heart failure. NHLBI intramural investigators have been examining the complex ways that energy conversion processes in the heart interact with muscle contraction and coronary blood flow. These investigators have made important contributions to the elucidation of the basic mechanisms involved in heart failure that may result ultimately in new strategies for diagnosis, prevention, and treatment of heart failure.

Vascular Biology and Coronary Restenosis

In 1992, over 360,000 angioplasties were perform in the U.S. Of those, 25 to 50 percent resulted in restenosis. It is believed that restenosis results when smooth muscle cells (SMC) are activated in response to injury, causing them to proliferate and migrate to the lesion. Intramural investigators have focused their attention on understanding the control of the SMC response to injury. They are examining the mechanisms underlying the restenosis process in order to develop new molecular-based strategies to prevent it. A genetically engineered recombinant toxin has been shown to be effective in inhibiting SMC proliferation in vitro. In addition, an adenoviral vector has been shown to be efficient and selective in transferring a foreign gene into SMCs in areas of vascular injury. Current efforts are concerned with designing adenoviruses that encode antiproliferative gene products to inhibit restenosis. If successful, they may be able to reduce substantially and perhaps even prevent post-angioplasty restenosis.

Bone Marrow Transplantation

Last year the NHLBI officially dedicated its Bone Marrow Transplant Unit. A program of autologous bone marrow transplantation for patients with multiple myeloma and chronic myelogenous leukemia has been initiated. Six patients received peripheral blood and bone marrow cells that were transduced with retroviral vector preparations. During the early post-transplantation stages, the presence of genetically modified cells was detected in their peripheral blood. The ultimate goal of these studies is to use gene transfer to create bone marrow resistant to myelosuppression by commonly used chemotherapeutic agents.

National Heart, Lung, and Blood Institute

RESEARCH MANAGEMENT AND SUPPORT

Authorizing Legislation - Section 301, 487, and Part C, Subpart 2 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
478	$56,719,000	465	$56,695,000	452	$57,385,000	-13	+$690,000

This document provides justification for the FY 1995 Non-AIDS activities of the National Heart, Lung, and Blood Institute. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The Research Management and Support budget activity provides funds for the overall management of the Institute's programs; for the education programs in the Office of Prevention, Education, and Control; and for international cooperative research activities. One of the most important uses for these funds relates to the coordination of activities that cut across program lines such as minority health and training, women's health issues, AIDS research, international cooperative research agreements, and administrative initiatives, for example, new agreements with the private sector authorized by the Federal Technology Transfer Act.

Funding for this program during the last five years has been as follows:

	Amount	FTEs
FY 1990	$50,039,000	442
FY 1991	51,646,000	471
FY 1992	56,903,000	486
FY 1993	56,719,000	478
FY 1994	56,695,000	465

Rationale for the Budget Request

The FY 1995 budget request for Research Management and Support is $57,385,000, an increase $690,000 from the FY 1994 level of $56,695,000.

National Center on Sleep Disorders Research

Establishing the National Center on Sleep Disorders Research within the NHLBI brings exciting prospects to the Institute's research portfolio. The Center will be the focal point for trans-NIH and interagency sleep research. The Center's first scientific initiative will focus on the cardiopulmonary consequences of sleep apnea. This initiative will determine the degree to which sleep apnea serves as risk factor for the development of cardiovascular and cerebrovascular disease. It will also examine possible associations between sleep apnea, hypertension, and stroke among different age, gender, and ethnic groups. Some very important initiatives for future sleep research include sleep education and collaborations with professional and voluntary organizations, local governments, and the Department of Transportation to examine the relationships between sleep apnea, fatigue, and auto accidents.

Administrative Reforms

The Institute is seeking new and different ways to manage its programs and implement the recommendations of the National Performance Review. A committee of senior Institute staff--the BOLD Committee--has enlisted the help of many Institute employees to find ways to save dollars, FTEs, and enhance the effectiveness of our programs. Among the options under review are possible reorganizations and consolidation of currently separated organizational units, changes in staffing patterns to accomplish certain functions, and ways to simplify how selected tasks are performed or even eliminate them altogether.

The extramural Divisions of the Institute, currently located at two separate off-campus sites in Bethesda, are moving into a single off-campus facility in early calendar year 1995. While this will not provide the advantages of an on-campus location, at least it will provide integration and consolidation of the extramural programs and supporting services.

Education Programs

The Office of Prevention, Education, and Control (OPEC) is taking important steps to reorganize in a project team management structure in accordance with the principles found in the recently released "National Performance Review". The office is seeking greater efficiencies in the operation of its national education programs while at the same time creating a new capacity to rapidly respond to advances in medical and public health science with appropriate communication efforts. The use of creative new "electronic highways" or dissemination systems based on public and proprietary networks and electronic bulletin boards could expedite the flow of information to professional and public audiences and enhance the utility of NHLBI information as a national resource. Our reorganization will help us take advantage of this new technology.

In order to accommodate other research translation and dissemination initiatives such as the newly created National Center on Sleep Disorders Research, the Office has had to make difficult decisions regarding phase out of two of its education programs. The National Blood Resource Education Program (NBREP) achieved the most important goals it set at its inception in 1987. One of those goals was to bring together a national group of interested

National Heart, Lung, and Blood Institute

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director..................	11	10	10
Office of Program Planning and Evaluation..........................	35	34	33
Office of International Programs.........	8	8	6
Office of Prevention, Education and Control...........................	36	34	33
Office of Administrative Management......	53	50	48
Division of Heart and Vascular Diseases..	71	69	68
Division of Epidemiology and Clinical Applications..................	82	80	78
Division of Lung Diseases................	32	31	30
Division of Blood Diseases and Resources..........................	33	32	31
Division of Intramural Research..........	433	420	407
Division of Extramural Affairs...........	117	117	115
Total, NHLBI........................	911	885	859

Average GS/GM Grade

1989...	9.96
1990...	10.00
1991...	10.04
1992...	10.05
1993...	10.03
1994...	10.00

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

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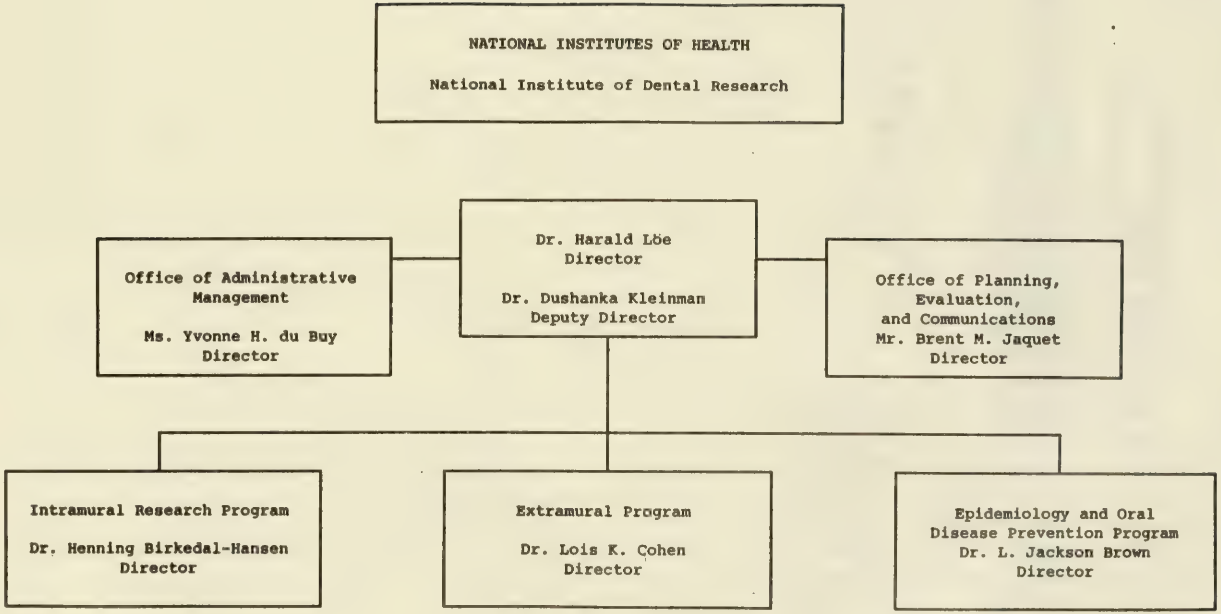
NATIONAL INSTITUTES OF HEALTH
National Institute of Dental Research
Dr. Harald Löe
Director
Dr. Dushanka Kleinman
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Office of Administrative Management
Ms. Yvonne H. du Buy
Director
Office of Planning, Evaluation, and Communications
Mr. Brent M. Jaquet
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Intramural Research Program
Dr. Henning Birkedal-Hansen
Director
Extramural Program
Dr. Lois K. Cohen
Director
Epidemiology and Oral Disease Prevention Program
Dr. L. Jackson Brown
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to dental diseases, [$169,520,000] *$163,776,000 of which $1,841,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriations Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Language Analysis

Language Provision	Explanation
"....of which $1,841,000 shall not become available for obligation until September 19, 1995."	To ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

National Institute of Dental Research

Amounts Available for Obligation [1]

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation....................	$163,269,000	$169,520,000	$163,776,000
Section 511 reduction at 0.8%...	-1,306,000	---	---
Section 216 S&E reduction.......	-651,000	---	---
Section 513 consultant services reduction....................	-11,000	---	---
Subtotal, adjusted appropriation............	161,301,000	169,520,000	163,776,000
Real transfer to:			
NIAID for tuberculosis research....................	-159,000	---	---
Comparative transfer to:			
Office of AIDS Research for HIV activities..............	-8,375,000	-11,431,000	---
Subtotal, adjusted budget authority................	152,767,000	158,089,000	163,776,000
Unobligated balance, lapsing....	-26,000	---	---
Total obligations............	152,741,000	158,089,000	163,776,000

---

[1] Excludes $57,000 for royalties received in 1993, and the following amounts for reimbursable activities carried out by this account: 1993 - $1,127,000; 1994 - $2,400,000; and 1995 - $2,400,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Mechanism

Research Grants:	1993 Actual No.	1993 Actual Amount	1994 Appropriation No.	1994 Appropriation Amount	1995 Estimate No.	1995 Estimate Amount
Research projects:						
Noncompeting	298	$56,895,000	278	$55,412,000	284	$56,083,000
Administrative supplementals	(32)	970,000	(33)	1,044,000	(33)	1,087,000
Competing projects:						
Renewals	40	8,194,000	50	12,129,000	42	10,698,000
New	53	7,745,000	55	8,804,000	59	10,306,000
Subtotal, competing	93	15,939,000	105	20,933,000	101	21,004,000
Subtotal, research projects	391	73,804,000	383	77,389,000	385	78,174,000
Research Centers:						
Specialized/comprehensive centers	28	17,452,000	28	18,505,000	27	20,991,000
Other Research:						
Research career programs	127	8,684,000	137	10,477,000	137	10,771,000
Minority biomedical support	--	77,000	--	186,000	--	196,000
Other research	78	3,169,000	42	2,118,000	78	3,178,000
Subtotal, other research	205	11,930,000	179	12,781,000	215	14,145,000
Total, research grants	624	103,186,000	590	108,675,000	627	113,310,000

Research Training:						
Individual awards:						
Noncompeting	11	289,000	16	500,000	10	314,000
Competing projects	11	325,000	2	56,000	8	257,000
Subtotal, individual	22	614,000	18	556,000	18	571,000
Institutional awards:						
Noncompeting	159	4,491,000	182	5,482,000	152	4,813,000
Competing projects	18	726,000	--	124,000	30	950,000
Subtotal, institutional	177	5,217,000	182	5,606,000	182	5,763,000
Total, research training	199	5,831,000	200	6,162,000	200	6,334,000
Research and development contracts	18	4,538,000	20	4,181,000	21	4,762,000
	FTEs		FTEs		FTEs	
Intramural research	274	29,193,000	274	29,193,000	263	29,129,000
Research management and support	88	10,019,000	88	9,878,000	88	10,241,000
Total	362	152,767,000	362	158,089,000	351	163,776,000
Clinical trials		(4,491,000)		(4,782,000)		(4,993,000)

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Summary of Changes

1994 Estimated budget authority	$158,089,000
1995 Estimated budget authority	163,776,000
Net Change	+5,687,000

Changes:	1994 Current Estimate Base		Change from Base	
A. Built-in:	(FTEs)	Budget Authority	(FTEs)	Budget Authority
1. Intramural:				
a. Annualization of January 1994 locality pay	---	$15,967,000	---	+$152,000
b. Within grade increases	---	15,967,000	---	+206,000
c. One less day of pay	---	15,967,000	---	-61,000
d. January 1995 pay increase	---	15,967,000	---	+192,000
e. FECF/unemployment comp	---	11,000	---	+1,000
f. Payment for centrally furnished services	---	6,136,000	---	+356,000
g. FTS increase	---	100,000	---	+4,000
h. Service and supply fund	---	4,341,000	---	+150,000
i. Increased cost of laboratory supplies, materials and other expenses	---	2,856,000	---	+82,000
Subtotal				1,082,000
2. Research Management & Support:				
a. Annualization of January 1994 locality pay		5,077,000		+54,000
b. Within grade increases		5,077,000		+74,000
c. One less day of pay	---	5,077,000	---	-20,000
d. January 1995 pay increase	---	5,077,000	---	+61,000
e. FECF/unemployment comp	---	80,000	---	+11,000
f. Payment for centrally furnished services	---	2,525,000	---	+221,000
c. DHHS Working Capital Fund		236,000	---	+2,000
g. FTS increase	---	---	---	+1,000
e. Service and supply fund increase		549,000	---	+25,000
f. Increased cost of laboratory supplies, materials and other expenses		1,727,000	---	+46,000
Subtotal				+475,000

Summary of Changes--Continued

	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting..........	278	$56,456,000	+6	+$714,000
b. Competing.............	105	20,933,000	-4	+71,000
Total..................	383	77,389,000	+2	+785,000
2. Research centers............	28	18,505,000	-1	+2,486,000
3. Other research...............	179	12,781,000	+36	+1,364,000
4. Research training............	200	6,162,000	--	+172,000
5. R&D contracts................	20	4,181,000	+1	+581,000
	FTEs		FTEs	
6. Intramural research.........	274	29,193,000	-11	-1,146,000
7. Research mgmt. & support....	88	9,878,000	---	-112,000
Subtotal...............				+4,130,000
Total changes........				+5,687,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	362	351	-11
Full-time equivalent of overtime and holiday hours	2	2	---
Average ES salary	$111,900	$113,200	+$1,300
Average GM/GS grade	9.8	9.8	---
Average GM/GS salary	43,500	44,000	+500
Average salary, grades est. by act of July 1, 1944 (42 USC 207)	74,300	75,200	+900
Average salary of ungraded positions	23,800	24,100	+300
Personnel compensation:			
Full-time permanent	$11,098,000	$11,434,000	+$336,000
Other than full-time permanent	4,462,000	4,175,000	-287,000
Other personnel services	430,000	444,000	+14,000
Special personnel services	1,588,000	1,634,000	+46,000
Total personnel compensation	17,578,000	17,687,000	+109,000
Personnel benefits	3,455,000	3,466,000	+11,000
Benefits to former personnel	11,000	11,000	---
Travel and transportation of persons	360,000	345,000	-15,000
Transportation of things	52,000	60,000	+8,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Rent, communications and utilities..	$547,000	$547,000	---
Printing and reproduction...........	152,000	152,000	---
Other services:			
Consultant services............	150,000	140,000	-10,000
Other services.................	1,244,000	983,000	-261,000
Purchases from Govt. accounts..	13,604,000	14,715,000	+1,111,000
R&D contracts..................	2,359,000	2,377,000	+18,000
Supplies and materials..............	2,161,000	2,159,000	-2,000
Equipment...........................	1,579,000	1,490,000	-89,000
Grants, subsidies & contributions...	114,837,000	119,644,000	+4,807,000
Total, budget authority........	158,089,000	163,776,000	+5,687,000

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIDR

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	11,098	11,098	11,434	336
11.3	Other than full-time permanent	4,462	4,462	4,175	(287)
11.5	Other personnel compensation	430	430	444	14
11.8	Special personnel services payments	1,588	1,588	1,634	46
11.9	Subtotal, personnel compensation	17,578	17,578	17,687	109
12.1	Civilian personnel benefits	3,455	3,455	3,466	11
13.0	Benefits for former personnel	11	11	11	0
	Subtotal Pay Costs	21,044	21,044	21,164	120
21.0	Travel and transportation of persons	354	360	345	(15)
22.0	Transportation of things	63	52	60	8
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	537	547	547	0
24.0	Printing and reproduction	168	152	152	0
25.0	Other Services	12,459	12,394	12,671	277
26.0	Supplies and materials	2,867	2,161	2,159	(2)
	Subtotal non-pay costs	16,448	15,666	15,934	268
	Total Administrative Costs	37,492	36,710	37,098	388

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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National Institute of Dental Research

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to Be Taken
1994 House Report	
Advanced Materials	
1. The House in its report 103-156, page 56, stated "The need for improved biomaterials has been heightened by concerns raised about the safety of a mercury-containing dental amalgams. Although the Public Health Service Committee to Coordinate Environmental and Related Programs issued a report earlier this year stating that amalgams posed no risk to the public except in rare cases of allergy, it asked the Institute to address the health effects of dental amalgams more fully and explore safe, economical alternatives. The Committee intends that a portion of the increase provided be directed toward amalgam research."	1. NIDR support of bioengineering research at NIST has led to the development of a new method for consolidating metals to produce mercury-free dental filling. CRADA has been negotiated with industry to commercialize the technology.
1994 Senate Report	
Amalgams	
1. The Senate in its report 103-143, page 85, stated "In January 1993, the U.S. Public Health Service Committee to Coordinate Environmental and Related Programs issued a report stating that amalgams posed no risk to the public except in rare cases of allergy. However, the panel asked the Institute to address the health effects of dental amalgams more fully and explore safe, economical alternatives."	1. Our epidemiologists are collaborating with the Air Force in a major health study to investigate the effects of mercury vapor in adults. To measure these effects, the investigators will document the the total dental amalgam years' exposure of veterans for whom there are extensive dental and medical records.

National Institute of Dental Research

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to Be Taken
1994 Senate Report	
Temporomandibular disorder	
2. The Senate in its report 103-143, page 85, stated "Temporomandibular disorder (TMD) is a common jaw disorder that can cause excruciating pain, difficulty in eating or talking, and other debilitating problems. Between 500,000 and 1 million new patients seek treatment for TMD every year; 80 to 90 percent of whom are women. The committee is aware that congressional investigations and clinical research have raised questions about the safety and effectiveness of certain treatments for TMD, including implants and grafts and urges NIDR to support research in this area."	2. The NIDR has recently developed new research diagnostic criteria for TMDs, which are being tested in clinical studies. The Institute is also supporting several new initiatives to stimulate TMD research, including an International Workshop on TMD and Related Pain Conditions scheduled for April 1994. These efforts and the expanded research agenda are expected to yield definitive guidelines for the diagnosis, treatment, and prevention of TMDs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation......	Section 301	42§241	Indefinite	$151,927,000	Indefinite	$157,442,000
National Institute of Dental Research.	Title IV, Part C, Section 453	42§285h 288c	Indefinite		Indefinite	
National Research Service Awards.....	Section 487(d)	42§288	$400,000,000	6,162,000	Such sums as necessary	6,334,000
Total Budget Authority				158,089,000		163,776,000

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NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$98,841,000	$97,691,000 2/	$103,728,000	$103,282,000
1986 Sequester				-4,441,000
1987 3/	96,482,000	116,275,000	116,553,000	117,945,000
1988	113,602,000	129,106,000 4/	131,559,000	126,297,000
1989	127,157,000 5/	127,315,000 6/	132,578,000	130,752,000
1990	131,527,000 7/	138,053,000	137,096,000	137,646,000
1990 Sequester				-1,897,000
1991	140,520,000	149,592,000 8/	151,057,000	148,918,000 9/
1991 Sequester				-2,000
1992	160,939,000	161,235,000	158,266,000	158,417,000 10/
1993	166,742,000	161,636,000	163,269,000	161,301,000 11/
1994	163,009,000	169,520,000	169,520,000	169,520,000
1995	163,776,000 12/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes $4,562,000 in NRSA training programs not considered.

3/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread the funding among the Institutes, including $2,733,000 for the National Institute of Dental Research.

4/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

5/ The request excludes funds for AIDS research and education ($3,562,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes $5,368,000 in NRSA training programs not considered.

7/ The request excludes funds for the National HIV Program ($4,269,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

8/ Excludes $5,893,000 in NRSA training programs not considered.

9/ Excludes enacted administrative reductions of $4,354,000.

10/ Excludes enacted administrative reductions of $1,753,000 and a rescission of $323,000.

11/ Excludes enacted administrative reductions of $1,968,000.

12/ The request excludes funds for HIV research activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Oral diseases and disorders research.		$106,378		$112,578		$113,553		$119,018		$124,406		$5,388
Intramural research....	262	26,412	277	28,768	274	29,180	274	29,193	263	29,129	-11	-64
Research management and support..........	73	9,687	84	9,400	88	10,008	88	9,878	88	10,241	--	363
Total obligations....	335	142,477	361	150,746	362	152,741	362	158,089	351	163,776	-11	5,687
Unobligated balance lapsing..............	--	11	--	17	--	26	--	---	--	---	--	---
Total, budget authority.	335	142,488	361	150,763	362	152,767	362	158,089	351	163,776	-11	5,687

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Dental Research

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
362	$152,767,000	362	$158,089,000	351	$163,776,000	-11	+$5,687,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of Dental Research (NIDR). Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

The National Institute of Dental Research supports research and research training "to improve the oral health of the American people"--a mission that has taken on special meaning in the 1990s as we emphasize ways to prevent disease in high risk groups, especially among the elderly, minorities, and people with medical conditions and medical treatments that compromise oral health. Forty-five years of research have confirmed the importance of oral health to general health and the value of using orofacial tissues to study other body systems and diseases. The result has been expanded research and new findings in relation to craniofacial genes and birth defects, bone and joint diseases, AIDS and immunity, oral cancer, chronic pain conditions, and epidemiology, behavior, biomaterials, and diagnostic systems.

The President's appropriation request of $163,776,000 for this account represents current law requirements. No proposed law amounts are included.

The Image of Pain

The latest neuro-imaging techniques show dramatic changes in the brain in response to pain. Our staff scientists, in collaboration with other NIH scientists, are using the advanced imaging resources in the NIH Clinical Center to produce some of the first films to show extensive brain changes in experimental and chronic pain. In positron emission tomography (PET) a radioactive tracer is introduced into the bloodstream. The regions of the brain that are most active receive the most tracer-rich blood flow and show up as brightly lighted areas in color-coded brain scans. Normal volunteers were tested at rest and under two test conditions: 1) when the hot-pepper ingredient capsaicin was injected under the skin of the forearm, and 2) an hour later, when subjects reported a spreading sensation of pain outside the region affected by capsaicin. A wide variety of sensory and limbic system centers (concerned with emotion and behavior) were illumined under the test conditions, with evidence that additional circuits were recruited in response to spreading pain. When patients with chronic pain affecting a limb were tested, there were notable changes in input from the affected limb to the thalamus--suggesting that this major coordinating center for sensory information plays an important role in modulating pain in chronic conditions. A second technique, functional magnetic resonance imagery (fMRI), produces high resolution images of the cortex without the use of radioactive tracers. The fMRI scans also show dramatic moment-to-moment changes in brain activity in the sensory cortex in response to pain. Future research will build upon these studies, with plans to modify fMRI technology to permit imaging the spinal cord, the point of entry into the central nervous system for pain signals from most parts of the body.

The Cost of Chronic Pain

Congressional concern for the economic, social, and personal costs of chronic pain has led to a request in the NIH Revitalization Act of 1993 for NIDR to take the lead in a report on the incidence and health care costs associated with seven chronic pain conditions. The report will be based on state-of-the-science papers from experts in the epidemiology and health care costs associated with each condition: low back pain due to injury; post-stroke pain; temporomandibular disorders; post-shingles neuralgia; phantom pain; reflex sympathetic dystrophy; and painful diabetic neuropathy. Review and development of the final report will be conducted by an interagency task force composed of representatives from NIDR and other NIH components and the Agency for Health Care Policy and Research.

Gene Therapy

The salivary glands are the targets for two exciting gene transfer experiments in animals. The first experiment aims to restore function to damaged glands; the second experiment aims at enhancing the ability of healthy glands to secrete anti-fungal compounds to treat candidiasis, a serious infection in AIDS and other immunosuppressed patients. Both experiments use modified cold viruses (adenoviruses) to transfer foreign genes directly into salivary gland ducts in rats. In order to restore function, the investigators need to transfer genes that will direct the conversion of salivary ductal cells into salt- and fluid-secreting cells. They have already cloned a gene that could render the cells permeable to water. To treat candidiasis, the genes transferred code for the production of a potent anti-candidal peptide (histatin), which is not normally produced in rats. This experiment has been successful. The glands in the treated rats produce messenger RNA and histatin. If further clinical testing shows that these approaches are safe and effective, the potential for benefit is huge: As many as a million patients suffer Sjögren's syndrome in which the salivary and tear glands are progressively destroyed; in addition, many thousands of patients suffer salivary gland damage as a result of radiation to the head or neck and chemotherapy to treat cancer. For immunosuppressed patients, or those with drug-resistant forms of candidiasis, the slow continuous release of a potent antifungal compound directly into the mouth should be an invaluable aid.

Mercury-Free Fillings

NIDR support of bioengineering research at the National Institute of Standards and Technology has led to the development of a new method for consolidating metals to produce a mercury-free dental filling. For over 150 years the standard "silver" filling has been a compound of metals such as silver and tin, amalgamated by mercury. While there is no scientific evidence that mercury in the amount used in fillings is harmful, concerns have been raised about toxicity. The new prototype avoids the use of mercury altogether. Instead, the metals are consolidated using processes called fast diffusion and cold welding. The bulk of the consolidation occurs when the filling is placed. The developers have engineered the process in such a way that the normal pressure a dentist applies to plug a traditional amalgam is all that is necessary to accomplish the welding. Several patent disclosures and a continuation to the original patent have been filed. A Cooperative Research and Development Agreement has been negotiated with industry to commercialize the technology.

Minority Health Centers

We are currently supporting six developmental Regional Research Centers for Minority Oral Health that target minority dental schools or schools serving large minority populations in San Antonio, Washington, New York, Newark, Nashville, and Los Angeles. In most cases the minority-based institution is collaborating with a research-intensive institution in efforts to improve minority health and increase the number of minority research investigators. Now in their third year, the centers have launched a number of studies including looking at lifestyle in relation to oral health; oral manifestations of HIV infection in minority groups; oral cancer (which affects blacks disproportionately); the relationship between periodontal disease and diabetes among Hispanic populations; and genetic and environmental aspects of cleft lip and cleft palate (more prevalent in some minority populations). In FY 1995, the developmental centers will compete for formal, full-scale research center grants; it is anticipated that three such awards will be made.

An Oral Health Clearinghouse

In January 1994, NIDR launched the first government-sponsored National Oral Health Information Clearinghouse (NOHIC) to serve the public and health care providers. The need for such a resource was signalled by growing numbers of patients whose health problems or treatments directly or indirectly affect their oral health. These "special care" populations include the parents of infants born with cleft lip or other facial birth defects; women newly diagnosed with Sjögren's syndrome; diabetic patients at risk for periodontal disease; and cancer patients receiving chemotherapy or radiation. These people not only need information about their condition and its treatment, but also information about where they can find knowledgeable oral health care providers. For practitioners, the need is for comprehensive information to better serve these patients. NOHIC services include maintaining a reference database of all oral health information publications and materials, and producing and distributing patient and provider education materials. The service is accessible by computer as well as by letter and telephone.

The President's appropriation request of $163,776,000 for this account represents current law requirements. No proposed law amounts are included. Fundings for the National Institute of Dental Research during the last five years has been as follows:

	Amount	FTE
FY 1990	$130,789,000	335
FY 1991	142,488,000	335
FY 1992	150,763,000	361
FY 1993	152,767,000	362
FY 1994	158,089,000	362

Purpose and Method of Operation

Extramural research and training are supported through seven program areas; and funding mechanisms include research project grants, research centers, other research grants, research training, and research and development contracts. Intramural research is conducted at eight laboratories, including a dental clinic and pain research unit located in the NIH Clinical Center and an Epidemiology and Oral Disease Prevention Program. The leadership and scientific direction of the Institute are funded through the activity entitled Research Management and Support.

Overall Budget Policy

The FY 1995 budget request for NIDR is $163,776,000, an increase of $5,687,000 or 3.4 percent over the comparable FY 1994 level of $158,089,000.

At the request level, the Institute will support 284 noncompeting research project grants at $56,083,000 and 101 new and competing renewal grants at $21,004,000, compared to 278 and 105, respectively, in FY 1994. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a 4-percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. The average cost of competing awards is expected to increase by 4.31 percent over the FY 1994 estimated average cost; this slight increase of 0.2 percent over the projected BRDPI of 4.11 percent is due to the anticipated receipt and award of several competing renewal aplications with unusually high average costs.

The other research grant category will be supported in FY 1995 at a total of $14,145,000 for 215 awards. The Institute will fund approximately 137 research career positions at $10,771,000; the Minority Biomedical Research Support Program will receive $196,000; and $3,178,000 will be available for other research related awards such as the small grant program, conference grants, small instrumentation grants, and scientific evaluation grants.

A total of $6,334,000 will support approximately 200 full-time training positions (FTTPs) in the National Research Service Awards program in FY 1995, compared to $6,162,000 for the same number of FTTPs in FY 1994. The average cost per trainee is increased by 2.8%.

Research and development contracts will be supported at $4,762,000, compared to $4,181,000 in FY 1994.

Support for intramural research, including the Institute's Epidemiology and Oral Disease Prevention Program, will be $29,129,000, a decrease of $64,000 from FY 1994. Research management and support activities will be funded at $10,241,000. The President's Budget request includes provisions for reducing full-time equivalent (FTE) positions by 11 FTEs in FY 1995. The NIDR request also incorporates the requisite provisions for administrative cost reductions in FY 1995.

National Institute of Dental Research

Extramural Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I.
1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$113,555,000	$119,018,000	$124,406,000	+$5,388,000

Research is focused on the causes, prevention, diagnosis, and treatment of diseases and abnormal conditions that affect the teeth, mouth, and jaws.

Funding for Oral Diseases and Disorders Research during the last 5 years has been as follows:

	Amount
FY 1990	$96,441,000
FY 1991	106,378,000
FY 1992	112,578,000
FY 1993	113,555,000
FY 1994	119,018,000

Rationale for the Budget Request

The FY 1995 budget request for this activity is $124,406,000, an increase of 4.5 percent over the FY 1994 estimate of $119,018,000. The following are a few examples of research activities to be funded in Oral Diseases and Disorders Research.

Jaw Pain and Dysfunction

NIDR is committed to furthering research on the temporomandibular disorders (TMDs)--conditions of pain and dysfunction in and around the jaw joint. Our studies indicate that these conditions are reported more often in women. In some cases individuals have undergone surgery to place a jaw implant--or to remove the implant in cases where it has failed. Given the current state of science, the NIDR has long advocated conservative approaches aimed at restoring function and relieving pain, and continues to support basic research to understand the causes and natural history of TMDs. One important result of this research has been the development of new research diagnostic criteria, using both physiological and psychological measures, to classify the TMDs into three major groups. The criteria are currently being tested in clinical studies, and results indicate that they are proving to be highly reliable and reproducible. Ultimately, using these criteria, researchers can effectively investigate surgical and non-surgical interventions.

We are also supporting several new initiatives to stimulate research. Principal among them is an International Workshop on the Temporomandibular Disorders and Related Pain Conditions scheduled for April 1994. This meeting, co-sponsored by the Office of Research on Women's Health, the National Institute of Arthritis and Muskuloskeletal and Skin Diseases, and the Agency for Health Care Policy and Analysis, with representatives from the Food and Drug Administration, will bring together a multidisciplinary group of world-class investigators in such areas as chronic pain, joint inflammatory and degenerative diseases, epidemiology, and behavioral science to delineate the state of the science and develop a research agenda. Representatives from TMD patient groups have been invited to attend, and participants will be provided with background materials derived from a number of ancillary meetings held over the past year, such as a Workshop on Biobehavioral Pain Research conducted in January 1994. Ultimately, these efforts and the expanded research agenda are expected to yield definitive patient and provider guidelines for the diagnosis, treatment, and prevention of TMDs.

Birth Defect Linked to Archaic Gene

A 600 million-year-old gene is responsible for a birth defect that occurs when the bony plates that make up the skull fuse too soon. There are at least 90 different forms of the condition, called craniosynostosis, 50 having a genetic cause. The more severely affected children may require multiple surgeries to relieve pressure on the brain and complications affecting breathing, vision, hearing. The latest discovery was based on genetic linkage studies of a large New England family which found a single base mutation on a gene called MSX2 on chromosome 5 in affected members. This gene lies in the domain of the so-called homeobox family of genes, a group of genes responsible for the basic organization of the embryo into head, trunk, and tail regions--from fly to fish to birds to man. Researchers believe that other mutations of MSX2 or similar homeobox genes may be involved in a variety of developmental abnormalities. Further research should provide insights into improved treatment and ultimately prevention.

A New Sugar Substitute

The quest for non-cariogenic non-caloric artificial sweeteners made recent headway with further development of "thaumatins"--a family of plant proteins with sweetness several thousand times more intense than sugar. Recombinant DNA technology has now been used to alter the composition of several thaumatins to improve their sweetness characteristics and stability. Tested in foods, these recombinant thaumatins were preferred over the natural products and have shown themselves to be stable over a wide range of temperatures for at least 2 years. Thus they represent an improvement over aspartame, whose drawbacks include heat lability and toxicity in certain individuals.

Therapeutic Liners and Coatings

Investigators are testing a thin cavity liner to be used under fillings to limit the progression of decay ("recurrent caries") which can lead to the need for a larger replacement filling and root canal problems. The liner reacts to acid--which signals the risk of further decay--and, depending on the formulation, either releases a warning dye or a caries-inhibiting agent. Other materials research is aimed at developing coating materials to protect tooth roots from caries. Current dental sealants that are used on the chewing esthetically acceptable thin coating material is needed, especially for older persons with receding gums or patients otherwise at high risk for decay.

Young and Minority Investigator Research Grants

We plan to use the increase in the "other research" mechanism in the FY 1995 budget to attract new young investigators to oral health research--particularly women and members of minority populations. These $50,000 awards are designed to allow investigators the time and funds to conduct pilot studies, learn techniques, or develop preliminary data in a research project that will allow them to compete successfully for a regular research project grant in the future.

Research Centers Program

Included in the 28 centers currently supported in FY 1994 are 6 developmental grants for Minority Health Centers. As explained earlier in this document, these developmental centers will compete for the award of three full-scale center grants in FY 1995. The FY 1995 request will also permit the award of two new specialized/comprehensive centers.

National Institute of Dental Research

Intramural Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I.
1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
274	$29,193,000	274	$29,193,000	263	$29,129,000	-11	-$64,000

Intramural research at the NIDR is conducted in eight laboratories and branches. A dental clinic and a pain research unit are maintained in the NIH Clinical Center to conduct research and diagnostics for patients. The Institute's intramural research budget activity also includes an Epidemiology and Oral Disease Prevention Program.

Funding for NIDR intramural research during the last 5 years has been as follows:

	Amount	FTEs
FY 1990	$25,274,000	262
FY 1991	26,423,000	262
FY 1992	28,785,000	277
FY 1993	29,193,000	274
FY 1994	29,193,000	274

Rationale for the Budget Request

The FY 1995 budget request for this activity is $29,129,000, a decrease of $64,000 from the FY 1994 estimate. The following are examples of research activities conducted in the NIDR intramural research program.

Women's Health

Estrogens and Inflammation. It is well known that women suffer more inflammatory diseases than men and that these conditions are often worsened during pregnancy (e.g., the swollen, inflamed gums of pregnancy gingivitis and exacerbations of autoimmune diseases such as lupus). Now our investigators have evidence that the female sex hormones, estrogen and progesterone, but not the male hormone, testosterone, increase the adhesion of white blood cells to the endothelial cells that line blood vessels. This is a critical step in the cascade of events that leads to the swelling, redness, and pain of inflammation. Future studies are aimed at understanding the variety of ways that female hormones modulate the immune system and developing ways to counter unwanted effects. It is also well known that circulating female hormones lower a woman's risk for heart disease. These protective effects also appear to stem from the estrogens' stimulating effects on endothelial cell adhesion, migration, growth, and formation of capillary-like blood vessels.

Sjögren's Syndrome. Our scientists are in the forefront of studies of Sjögren's Syndrome, an autoimmune disorder thought to affect at least one million Americans, predominantly women. The primary form of the disease is characterized by dry mouth and dry eyes caused by the progressive destruction of the salivary and tear glands. Other mucous membrane surfaces also experience drying. Secondary Sjögren's syndrome adds the complication of a connective tissue disorder, such as lupus or rheumatoid arthritis. The need to find better treatments for this devastating disorder has led our researchers to test combinations of drugs: a "secretogogue" to stimulate gland secretion, and an anti-inflammatory/anti-rheumatoid agent to decrease the autoimmune response. The investigators' long-term goal is to understand how and why the glands are destroyed. These efforts focus on T lymphocytes--immune cells that produce a number of factors called cytokines that have multiple effects on other cells. It now appears that one cytokine, interferon gamma, can stop salivary cell growth. Understanding that process could lead to the development of drugs to block glandular destruction and thus provide relief to many patients affected.

Acyclovir Suppresses Recurrent Cold Sores

Frequent occurrences of oral herpes simplex virus infections (cold sores) affect nearly one-third the U.S. population with an annual incidence estimated at 100,000,000 episodes. Although the anti-viral drug acyclovir has been used to treat genital herpes, it has never been thoroughly tested for its efficacy in suppressing oral herpes. A double-blind placebo-controlled study reported by our intramural scientists showed that acyclovir, twice daily, resulted in over a 50-percent reduction in the number of clinical occurrences and over a 70-percent reduction in the isolation of virus compared with placebo controls.

Oral Cancer

Cancer studies have benefited greatly from the discovery of biomarkers associated with tumor growth or suppression. These include the so-called cancer genes (proto-oncogenes) as well as tumor-suppressing genes, along with cell factors such as stress proteins, growth factors, and enzymes related to metastatic tumor growth. These studies have provided the rationale for the use of beta-carotene and vitamin E to reduce the risk of a premalignant oral lesion from developing into frank oral cancer. So promising is this approach that EODPP scientists are not only studying the mechanisms of action of these factors, but also determining which markers may be the most useful and reliable so as to enhance the sensitivity of clinical trials evaluating chemopreventive drugs. Our investigators are also looking for genetic markers that could be used in genetic screening studies. This could lead to earlier interventions with the potential for reversing the cancerous process.

In related clinical studies, scientists in our Epidemiology and Oral Disease Prevention Program (EODPP) are collaborating with National Cancer Institute scientists to study the effects of alternative therapies to manage oral and pharyngeal cancer among elderly patients. The project will also estimate the lifetime costs associated with these cancers.

A second clinical study, also in collaboration with NCI, will explore how suspected biomarkers associated with oral cancer may vary in an area known to have a relatively high prevalence of oral cancer: Puerto Rico. This is a follow-up study to a case-control investigation (i.e., where individuals with oral cancer--the "cases"-- are compared with individuals matched by age, sex, and other variables, but who do not have cancer--the "controls"). Among the factors being examined are the use of tobacco, alcohol, other aspects of the diet, oral health status, and the presence of papillomavirus.

Mercury Effects Study

Our epidemiologists are collaborating with the Air Force in a major study to investigate the potential adverse health effects of mercury vapor in adults. To measure these effects, the investigators will document the total dental amalgam years' exposure of veterans for whom dental and medical records have been compiled over the years. The oral health component of the study, conducted in late 1992 and early 1993, aims to define more precisely the human dose-response relationship between low levels of inorganic mercury exposure and potential effects on kidney, immune system, endocrine, and nervous system function. Oral examinations and urine and blood mercury assays have been completed and plans for analysis of the oral health and mercury concentration data have been submitted to Air Force senior research staff for review. Analytical collaboration efforts are expected to begin this year.

Schoolchildren's Survey

EODPP staff are completing plans for the next major national survey of the oral health of American schoolchildren between 5 and 17 years old. The survey, scheduled to be conducted during the 1996-97 school year, will provide a third set of data points to allow analysis of trends since the early 1980s. Every effort is being made to allocate the sample size so that estimates may be developed for whites, blacks, and Hispanics.

National Institute of Dental Research

Research Management and Support

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I.
1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
88	$10,019,000	88	$9,878,000	88	$10,241,000	--	+$363,000

This activity provides the leadership and management direction of the entire Institute in addition to the administrative management and scientific direction in the review, award, and monitoring of all extramural awards. Associated with this activity is the immediate Office of the Director and the Institute's program and administrative staff.

Funding for this activity during the last 5 years has been as follows:

	Amount	FTEs
FY 1990	$9,074,000	73
FY 1991	9,687,000	73
FY 1992	9,400,000	84
FY 1993	10,019,000	88
FY 1994	9,878,000	88

Rationale for the Budget Request

The FY 1995 budget request for research management and support (RMS) is $10,241,000, an increase of $363,000 over the FY 1994 level. The request allows for inflationary increases of $475,000, less administrative cost reductions of $112,000. The RMS activity will continue to provide leadership, program guidance, planning and evaluation, and overall administration for the programs and information directed to scientists, dental practitioners, and the public, in addition to continuing to administer, manage, and review the Institute's grant and contract programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Detail of Full-time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director..........	8	8	8
Office of Administrative Management....................	19	19	19
Office of Planning, Evaluation, and Communications............	22	22	22
Extramural Program..............	39	39	39
Epidemiology and Oral Disease Prevention Program............	43	43	43
Intramural Research Program.....	231	231	220
Total, NIDR................	362	362	351

Average GS/GM Grade

1990................	9.8
1991................	9.7
1992................	9.6
1993................	9.8
1994................	9.8
1995................	9.8

NOTE: Includes FTEs associated with HIV research activities. Funds to support theses FTEs are included in the NIH Office of AIDS Research.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FISCAL YEAR 1995

Volume IV

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Neurological Disorders and Stroke
National Institute of Allergy and Infectious Diseases
National Institute of General Medical Sciences

Justification of Estimates for Appropriations Committees

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

	FY 1995 Estimate		Page Number
	FTEs	Amount	
National Institute of Diabetes and Digestive and Kidney Diseases.....	642	$731,500,000	1
National Institute of Neurological Disorders and Stroke..............	696	630,443,000	51
National Institute of Allergy and Infectious Diseases...............	1,111	542,864,000	97
National Institute of General Medical Sciences..................	184	882,189,000	137

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1995 Budget	Page No.
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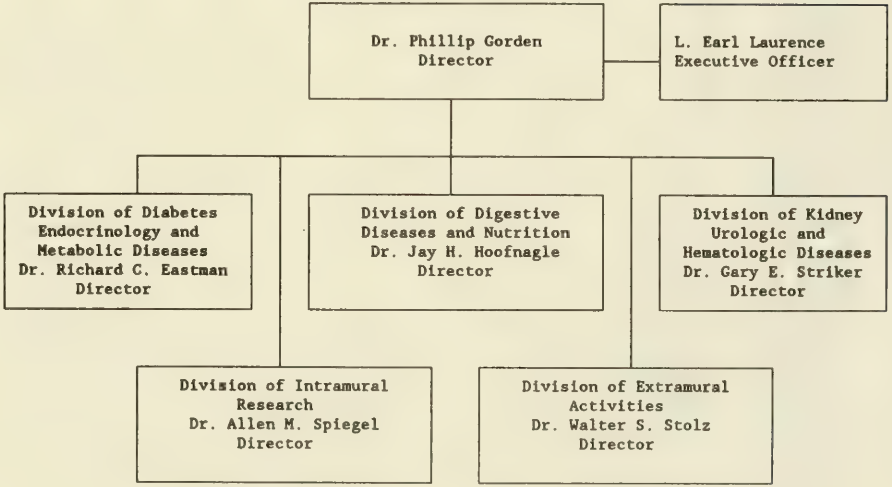
NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Organization Structure


Dr. Phillip Gorden
Director
L. Earl Laurence
Executive Officer
Division of Diabetes Endocrinology and Metabolic Diseases
Dr. Richard C. Eastman
Director
Division of Digestive Diseases and Nutrition
Dr. Jay H. Hoofnagle
Director
Division of Kidney Urologic and Hematologic Diseases
Dr. Gary E. Striker
Director
Division of Intramural Research
Dr. Allen M. Spiegel
Director
Division of Extramural Activities
Dr. Walter S. Stolz
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, [$716,054,000] $731,500,000 *of which $7,769,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriation Act, 1994.)*

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NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Language Analysis

Language Provision	Explanation
"......of which $7,769,000 shall not become available for obligation until September 19, 1995."	To ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation[1/]

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation:			
Annual	$688,633,000	$716,054,000	$731,500,000
Investment Initiatives			
Enacted rescission			
Section 214 travel reduction			
Section 216 salaries & expenses reduction	-1,748,000		
Section 511 8% reduction	-5,509,000		
Section 513 consultant services reduction	-34,000		
Section 513(a) travel reduction			
Section 513(a) S & E reduction			
Proposed rescission			
Subtotal, adjusted appropriation	681,342,000	716,054,000	731,500,000
Real transfer to:			
NIAID for tuberculosis research	-670,000	---	---
Comparative transfer to:			
Office of AIDS Research for HIV activities	-6,446,000	-10,438,000	---
Subtotal, adjusted budget authority	674,226,000	705,616,000	731,500,000
Unobligated balance lapsing	-158,000	---	---
Total, Obligations	674,068,000	705,616,000	731,500,000

[1/] Excludes the following amounts for reimbursements: FY 1993 - $8,827,000 and 3 FTE; FY 1994 - $10,000,000 and 5 FTE; and 1995 - $10,300,000 and 7 FTE."

Note: Excludes $72,000 for Royalties in FY 1993 and $81,000 in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting	1,645	363,338,000	1,610	355,284,000	1,390	349,417,000
Administrative supplementals	(110)	4,829,000	(41)	1,559,000	(41)	1,595,000
Competing						
Renewal	192	45,301,000	184	45,198,000	216	55,239,000
New	272	44,337,000	260	74,954,000	321	90,177,000
Supplemental	1	2,000	1	2,010,000	1	2,020,000
Subtotal, competing	465	89,640,000	445	122,162,000	538	147,436,000
Subtotal, research projects	2,110	457,807,000	2,055	479,005,000	1,928	498,448,000
Research centers						
Specialized/Comprehensive centers	60	46,023,000	61	50,102,000	61	52,161,000
Other Research						
Research career programs	168	15,195,000	213	17,576,000	213	18,068,000
Cooperative clinical research						
Minority biomedical research support		1,659,000		1,745,000		1,794,000
Other research related	53	2,469,000	64	2,430,000	64	2,498,000
Subtotal, other research	221	19,235,000	277	21,751,000	277	22,360,000
Total, research grants	2,391	523,153,000	2,393	550,858,000	2,266	572,969,000

Training						
Individual awards:						
Noncompeting	80	2,377,000	76	2,445,000	113	3,813,000
Competing	71	2,060,000	64	2,113,000	27	872,000
Subtotal, Individual	151	4,437,000	140	4,558,000	140	4,685,000
Institutional awards						
Noncompeting	616	18,058,000	576	18,941,000	573	19,189,000
Competing	98	2,929,000	152	4,444,000	155	4,851,000
Subtotal, Institutional	714	20,987,000	728	23,385,000	728	24,040,000
Total, training	865	25,424,000	868	27,943,000	868	28,725,000
Research and development contracts	33	19,148,000	42	20,569,000	42	21,145,000
	FTEs		FTEs		FTEs	
Intramural research	460	82,449,000	480	81,841,000	462	83,431,000
Research management and support	178	24,052,000	180	24,405,000	180	25,230,000
Total	638	674,226,000	660	705,616,000	642	731,500,000
Clinical Trials		(46,633)		(81,000)		(62,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

1994 Estimated budget authority	$705,616,000
1995 Estimated budget authority	731,500,000
Net change	+ 25,884,000

	1994 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Changes:				
A. Built-in:				
Intramural Research:				
1. One less day of pay		$35,683,000		-137,000
2. January 1995 pay increase		35,683,000		+428,000
3. Annualization of January 1994 pay increase		35,683,000		+378,000
4. Within-grade increase		35,683,000		+410,000
5. FECF		165,000		-21,000
6. Increased cost of centrally furnished services		23,754,000		+976,000
7. Increased cost of service and supply fund		11,808,000		+480,000
8. Increased cost of supplies and materials		10,596,000		+314,000
9. FTS				+7,000
Subtotal				+2,877,000
Research Management and Support:				
1. One less day of pay		$10,641,000		-41,000
2. January 1995 pay increase		10,641,000		+128,000
3. Annualization of January 1993 pay increase		10,641,000		+113,000
4. Within-grade increase		10,641,000		+164,000
5. DHHS Working Capital Fund		660,000		+5,000
6. Increased cost of centrally furnished services		5,072,000		+409,000
7. Increased cost of service and supply fund		4,688,000		+183,000
8. Increased cost of supplies and materials		4,004,000		+112,000
9. FTS				+2,000
Subtotal				+1,075,000

	No.	Amount	No.	Amount
B. Program:				
1. Research project grants........				
a. Noncompeting................	1,610	356,843,000	-220	-5,831,000
b. Competing..................	445	122,162,000	+93	+25,274,000
Total......................	2,055	479,005,000	-127	+19,443,000
2. Research centers..............	61	50,102,000	---	+2,059,000
3. Other research................	277	21,751,000	---	+609,000
4. Training......................	868	27,943,000	---	+782,000
5. Contracts.....................	42	20,569,000	42	+576,000
6. Intramural Research...........	480	81,841,000	-18	-1,184,000
7. Research Management and Support	180	24,405,000	---	-353,000
Subtotal....................				+21,932,000
Total changes................				+25,884,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment.....	660	642	-18
Full-time equivalent of overtime and holiday hours................	4	5	+1
Average ES salary....................	$108,883	110,625	+1,742
Average GM/GS grade..................	$ 10.5	10.5	---
Average GM/GS salary.................	$ 47,067	48,130	+1,063
Average salary, grades est. by act of July 1, 1944 (42 USC 207)..........	$ 83,324	84,538	+1,214
Average salary of ungraded positions..	$ 23,041	23,502	+461
Personnel compensation:			
Permanent positions................	22,632,000	23,551,000	+919,000
Positions other than permanent......	9,265,000	9,460,000	+195,000
Other personnel compensation........	1,640,000	1,744,000	+104,000
Special personal services...........	5,000,000	5,156,000	+156,000
Subtotal, personnel compensation..	38,537,000	39,911,000	+1,374,000
Personnel benefits...................	7,654,000	7,739,000	+85,000
Benefits for former personnel.........	26,000	26,000	---
Travel and transportation of persons..	1,050,000	1,100,000	+50,000
Transportation of things..............	185,000	150,000	-35,000

Budget Authority by Object - cont'd

	1994 Appropriation	1995 Estimate	Increase or Decrease
Rental payments to GSA................	---	---	---
Rental payments to others.............	---	---	---
Communications, utilities, and miscellaneous charges..........	1,600,000	1,850,000	+250,000
Printing and reproduction.............	350,000	350,000	---
Consulting services...................	300,000	315,000	+15,000
Other services........................	5,268,000	7,640,000	+2,372,000
Purchases from Government Accounts....	41,967,000	40,944,000	-1,023,000
Operation of GOCOs....................	---	---	---
R & D Contracts.......................	17,569,000	17,645,000	+76,000
Supplies and materials................	8,241,000	7,836,000	-405,000
Equipment.............................	4,068,000	4,300,000	+232,000
Grants, subsidies and contributions...	578,801,000	601,694,000	+22,893,000
Insurance claims and indemnities......			
Interest and dividends................			
Total......................	705,616,000	731,500,000	+25,884,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIDDK

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	22,632	22,632	23,551	919
11.3	Other than full-time permanent	9,265	9,265	9,460	195
11.5	Other personnel compensation	1,640	1,640	1,744	104
11.8	Special personnel services payments	5,000	5,000	5,156	156
11.9	Subtotal, personnel compensation	38,537	38,537	39,911	1,374
12.1	Civilian personnel benefits	7,654	7,654	7,739	85
13.0	Benefits for former personnel	26	26	26	0
	Subtotal Pay Costs	46,217	46,217	47,676	1,459
21.0	Travel and transportation of persons	1,050	1,050	1,100	50
22.0	Transportation of things	185	185	150	(35)
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	1,600	1,600	1,850	250
24.0	Printing and reproduction	350	350	350	0
25.0	Other Services	44,535	41,234	42,098	864
26.0	Supplies and materials	8,241	8,241	7,836	(405)
	Subtotal non-pay costs	55,961	52,660	53,384	724
	Total Administrative Costs	102,178	98,877	101,060	2,183

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item

1994 House Report

Diabetes	Action Taken or to be Taken
1. The House in its report 103-156, page 56, stated..."NIDDK is the lead agency of the Federal government for research efforts to combat diabetes mellitus and its complications. Diabetes is the sixth leading cause of death from disease in the U.S., afflicting an estimated 13 to 14 million people, but approximately one-half of these cases are undiagnosed. It is also the leading cause of new adult blindness, kidney failure, and non-traumatic amputation, and is a major risk factor for stroke, heart attack, and premature death. The annual economic cost to the nation of diabetes is estimated to be $20 to $25 billion. The Committee has given research and prevention activities related to diabetes the highest priority throughout the bill and expects NIDDK to use the increased resources provided to expand this critical research. This includes a substantial effort to find the genetic defect which is likely to be responsible for certain forms of diabetes and which may be the basis for vulnerability in all diabetes cases."	1. Having recently completed the very successful 10-year landmark Diabetes Control and Complications Trial, the NIDDK in FY 1994 has begun a major new program activity, called the Diabetes Prevention and Treatment Initiative, which consists of multiple components encompassing basic and clinical research, clinical studies and trials, and national multicenter trials for the prevention of adult-onset and juvenile diabetes. In addition, the NIDDK greatly expanded emphasis on the search for diabetes genes in FY 1993, and will continue to give high priority to new and exciting future opportunities in this area.
Bionutrition	
2. The House in its report 103-156, pages 56-57, stated..."NIDDK is the lead Institute within the NIH for nutrition research. The	2. Bionutrition efforts are underway in a number of NIH institutes. In addition to these individual institute activities, NIH-wide

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Item	Action Taken or to be Taken
1994 House Report	
Bionutrition	
Committee has heard convincing testimony on the importance and potential benefits of this area of investigation for many diseases including cancer and heart disease. The Committee believes that the increase provided will permit continued expansion of nutrition research, including the important work in the area of obesity. This is also critical to efforts in the area of women's health.	research in this area is coordinated through the NIH Nutrition Coordinating Committee (NCC), which comprises representatives of all the NIH institutes and liaisons from other Federal agencies. Recently the functions of the NCC and of the NIH Division of Nutrition Research Coordination were transferred from the Office of the Director, NIH, to the NIDDK Director's Office, consistent with the NIH Revitalization Act emphasis on the NIDDK role in nutrition research and coordination. Through the NCC, the NIDDK will lead in promoting trans-NIH research solicitations in bionutrition and other timely areas of nutrition research. In addition, a diverse group of outside experts will be convened to help in assessing the most compelling opportunities in bionutrition. Through the NCC, the NIH also will begin a dialogue on nutrition training that will involve intramural and extramural components, and will address the training recommendations of the recent Institute of Medicine report on "Opportunities in the Nutrition and Food Sciences." This report was co-sponsored by several of the NIH institutes.
Molecular hematology	
3. The House in its report 103-156, page 57 stated..."The Committee is pleased by the early response	3. Seven exploratory grants (P20) were funded in fiscal year 1993 for the planning of Centers of

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Item

1994 House Report

Molecular Hematology	**Action Taken or to be Taken**
from the research community to the Institute's expanded efforts in the area of molecular hematology. The Committee believes the research can be helpful in a wide array of diseases such as sickle cell anemia and Cooley's anemia and has broad implications for the whole area of genetic blood disorders. The Committee urges the Institute to continue this initiative using all available mechanisms."	Excellence in Molecular Hematology. In fiscal year 1994, the Institute plans to establish up to three full-scale Centers (P50). Up to $2.2 million will be made available in fiscal year 1994 for the funding of these Centers.
Kidney disease	
4. The House in its report 103-156, page 57 stated..."The Committee believes that it would be an appropriate investment to expand research into the genetic basis, pathogenesis and treatment of this disease using all available mechanisms." [polycystic kidney disease]	4. In FY 1993, the NIDDK expended more than $5 million on research relevant to PKD. This research focuses on understanding the genetics of the disorder, its clinical manifestations, and its pathogenesis, as well as on following up leads for potential treatments.
5. The House in its report 103-156, page 57 stated..."The Committee is also concerned about the impact of kidney disease on children. The most common reason for the development of chronic kidney disease is childhood diabetes. The Committee supports increased research on the relationship of juvenile diabetes and adult kidney failure. The Committee is also concerned that NIDDK address the critical problem of the difficulties which occur in carrying out successful kidney transplants in children."	5. The Institute continues to support research related to kidney disease from childhood diabetes, including follow-up of an NIDDK-supported study showing that a medication commonly prescribed for hypertension can significantly protect the kidneys of people with juvenile diabetes. The NIDDK also supports research on kidney transplantation which should provide information regarding transplantation in children as well as adults. In addition, the Institute is continuing to expand its recently

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Item	Action Taken or to be Taken
1994 House Report	
Kidney Disease	initiated pediatric nephrology program, which will encourage all areas of kidney research affecting children, including the issues regarding diabetes and transplantation.
Urology	
6. The House in its report 103-156, page 57 stated..."Within the additional funding provided for the Institute, the Committee urges NIDDK to expand research into these new areas" [endocrine and related systems as they relate to prostate growth].	6. The Institute continues to support a significant amount of basic research on prostate growth. Much of this research was initiated as a result of Requests for Applications issued in fiscal years 1992 and 1993. In addition, three new George M. O'Brien Kidney and Urological Research Centers were established in fiscal year 1993 to focus on understanding prostate growth. The Institute currently supports a pilot clinical trial on the treatment of benign prostatic hyperplasia. This pilot trial, and the full-scale trial to begin in fiscal year 1995, will also provide new insights into endocrine factors in benign prostate hyperplasia.
7. The House in its report 103-156, page 57 stated..."Urinary incontinence, urinary tract infections and interstitial cystitis (IC) are significant urological health problems which affect primarily women. The Committee is pleased with the establishment of the IC database and encourages the Institute to continue to support basic research on understanding IC and to expand basic bladder research	7. The Institute plans to reissue a 1993 Request for Applications for basic research on interstitial cystitis and other bladder disorders of women. The Request for Applications specifically mentions IC, urinary incontinence, and urinary tract infections. This Institute will make available up to $1.5 million to fund new research in these areas.

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item	Action Taken or to be Taken
1994 House Report	
Urology	
on urinary incontinence and urinary tract infections."	
1994 Senate Report	
Digestive Diseases	
1. The Senate in its report 103-143, p. 86, stated..."The Committee is encouraged to hear that NIDDK-supported research is utilizing molecular genetic techniques to study Wilson's disease and hemochromatosis. Another area of great promise is in studying the role of helicobacter pylori bacterium in several types of ulcers. The Committee encourages NIDDK to continue efforts to develop the appropriate balance between conducting basic studies on digestive diseases and bringing this critical knowledge gained to the bedside to improve patient care."	1. NIDDK-supported research is continuing to utilize molecular techniques to study Wilson's disease and hemochromatosis. Two research groups are currently competing to identify and clone the gene(s) responsible for Wilson's Disease. Investigators are using two approaches to study hemochromatosis. The first approach is to diagnose the inherited disorder. Initial studies indicate that hereditary hemochromatosis may be associated with other forms of liver disease. The second avenue is to identify the primary hemochromatosis gene. It has been suggested that approximately one to two years will be needed to pin down the location of the hemochromatosis gene. The NIDDK issued a Program Announcement in August 1993 with the NIAID to encourage research in the role of Helicobacter pylori in duodenal ulcers, infection and gastritis. A consensus development conference sponsored by OMAR and the NIDDK is also planned for February 7-9, 1994 to examine data on H. pylori and peptic ulcer disease. Based on advances in basic

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

Item	Action Taken or to be Taken
1994 House Report Digestive Diseases	research, the Institute plans to issue a PA or RFA every two years to evaluate new interventions or therapies for digestive diseases in prospective, randomized, controlled clinical trials. Funding of applications will be based on the outcome of merit review under the peer review system.
Inflammatory Bowel Disease 2. The Senate in its report 103-143, p. 86, stated..."Additional funding to NIDDK is necessary to continue or supplement existing programs and train new investigators in IBD; establish fundamental resources for IBD research, such as the development of animal models, a cell-line gene bank, and disease-specific epithelial cell lines; and promote collaborations between IBD researchers and scientists from other selected disciplines."	2. The Institute plans to issue an RFA for fellowships and career awards in inflammatory bowel disease (IBD) in FY 1994. In addition, the Institute is committed to expanding its research portfolio in IBD through regular investigator-initiated research grants. The funding of all applications will be based on the extent of their merit as determined by the peer review system. A symposium is also being planned on IBD for 1994, sponsored by the NIDDK and the World Congress of Gastroenterology.
Hematology 3. The Senate in its report 103-143, pages 86-87 stated..."Last year the Committee encouraged the Institute to move forward to develop a program of centers of excellence in molecular hematology. The Committee is pleased to note that the Institute has completed that process and planning grants have been awarded to institutes of the	3. The Institute plans to establish up to three full-scale Centers of Excellence in Molecular Hematology in fiscal year 1994. Up to $2.2 million will be made available in fiscal year 1994 for the funding of these Centers.

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

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1994 House Report

Item	Action Taken or to be Taken
Hematology	
highest caliber. The Committee continues to be strongly supportive of the development of such centers, and encourages the NIDDK to establish a full centers program. The Committee urges the Institute to provide additional funds to this program beyond the necessary increases for ongoing hematology research programs.	
4. The Senate in its report 103-143, page 87 stated..."The Institute supports research on oral chelators for patients with Cooley's anemia and other anemias to reduce the iron overload caused by frequent blood transfusions, as well as on drugs which show promise in ameliorating the anemia itself. The Committee urges the Institute to continue its strong support of these efforts."	4. The Institute continues to support preclinical toxicity testing of potential oral iron chelators, as well as research on drugs which show promise in ameliorating Cooley's anemia and sickle cell anemia. Clinical studies of two promising drugs are continuing. Intramural scientists are developing an in vitro method for more rapid screening of new candidate drugs.
Kidney diseases	
5. The Senate in its report 103-143, page 87 stated..."The Committee is pleased that the NIDDK has followed past congressional directives for increasing kidney programs within the Institute, including the establishment of four additional George M. O'Brien and Urological Research Centers in 1993. The Committee expect this growth in kidney programs to continue, due to the medical and economic burden of these diseases."	5. In FY 1993, five additional George M. O'Brien Kidney and Urological Research Centers were funded: two additional kidney centers and three additional urology centers were funded. The NIDDK now supports a total 12 George M. O'Brien Kidney and Urological Research Centers: seven focusing on kidney research and five focusing on urology research. In addition, the Institute supports two Research Centers of Excellence in Pediatric Nephrology and Urology.

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Item	Action Taken or to be Taken
Kidney Diseases	
6. The Senate in its report 103-143, page 87 stated..."The Committee is also concerned about the status of advanced research training for young investigators, particularly for those in years 3 to 5. This uncertainty of obtaining funding is forcing a generation of young men and women to reevaluate whether they can financially afford a career in this area, and we are losing many of our best and brightest prospects. Unless NIDDK alters this situation, we will continue to lose bright, young investigators to other career paths. The Committee urges the Institute to provide additional support for the appropriate K series training awards."	6. The Institute has issued a Request for Applications entitled "Support of Minority Scientists in Kidney, Urology, and Hematologic Research. This Request is aimed primarily at recently trained M.D. and/or Ph.D. minority investigators and will assist the awardee to accept a tenure-earning position, gain additional research experience, and obtain preliminary data on which to base a subsequent research grant application. Support will be provided through the Small Grants (R03) program. The period of support is 1-2 years, with direct costs requested not to exceed $50,000 per year. The Institute anticipates making five awards in fiscal year 1994. In fiscal year 1993, the NIDDK began to support urologic research training of M.D./Ph.D. candidates in a joint program with the American Foundation for Urologic Research. This pilot K-series award program has the specific intent of providing opportunities for research and financial assistance.
IgA nephropathy	
7. The Senate in its report 103-143, page 88 stated..."The Committee believes that the NIDDK should support basic research into the pathogenesis and immunology of this IgA nephropathy, initiate research aimed at preventing the progression of the disease, and	7. The Institute has issued a Request for Applications for IgA nephropathy research. This initiative solicits both basic research and pilot clinical research on treatments for IgA nephropathy. Up to $2 million will be made available to fund

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Item	Action Taken or to be Taken
1994 House Report	
IgA nephropathy	
consider action to improve renal data, including the establishment of a data base on IgA nephropathy."	five to six meritorious applications in fiscal year 1994.
Kidney rehabilitation	
8. The Senate in its report 103-143, page 88 stated..."The Committee notes that the National Kidney and Urologic Disease Advisory Board will be sponsoring a workshop on rehabilitation of people with kidney failure. This condition is expensive to the Nation and neglected in rehabilitation research and practice. The advisory board is to be commended for its initiative, and the Committee encourages the Institute to fund this workshop."	8. This workshop will be held March 7-9, 1994. The NIDDK has participated in the planning and funding of this workshop and will assist in its implementation.
[Polycystic kidney disease (PKD)]	
9. The Senate in its report 103-143, page 88 stated..."Polycystic kidney disease is one of the most common hereditary disorder.... The Committee encourages the Institute to expand support of research to isolate and clone the genes and to search for novel therapeutic approaches to slow the progression of PKD."	9. In FY 1993, the NIDDK expended more than $5 million on research relevant to PKD. This research focuses on understanding the genetics of the disorder, its clinical manifestations, and its pathogenesis, as well as on following up leads for potential treatments.
[Diabetes]	
10. The Senate in its report 103-143, page 88, stated..."Native Hawaiians continue to experience extraordinary rates of diabetes. Accordingly, the Committee urges	10. The NIDDK has received applications solicited in response to a request for applications (RFA) entitled "Interventions in Diabetes Among

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1994 House Report

Polycystic Kidney Diseases (PKD)	Action Taken or to be Taken
NIDDK to develop a specific intervention program for this native American population."	Minority Populations." Two applications were received that proposed utilizing the Native Hawaiian population. Also, the NIDDK has received applications solicited in response to a RFA entitled "Non-Insulin-Dependent Diabetes Mellitus Primary Prevention Trial." Two applications utilizing Native Hawaiians have been submitted in response to this RFA. It is the intention of the NIDDK that 50 percent of the subjects enrolled in this trial will be minorities and will include Native Hawaiians.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation............	Section 301	42§241	Indefinite		Indefinite	
				$677,673,000		$702,775,000
National Institute of Diabetes and Digestive and Kidney Diseases......	Title IV, Part Section 453	42§285h 288c	Indefinite		Indefinite	
National Research Service Awards...........	Section 487(d)	42§288	$400,000,000	27,943,000	Such sums as necessary	28,725,000
Total Budget Authority.....				705,616,000		731,500,000

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1984	$426,394,000	$442,255,000 2/	$442,832,000 2/	$460,923,000
1985	475,324,000	515,516,000 3/	545,551,000	543,576,000
1986 4/	519,1858,000	541,298,000 5/	565,924,000	569,340,000
1986 Sequester				-24,482,000
1987	418,971,000	515,455,000	502,628,000	511,124,000
1988	440,504,000	563,768,000 6/	549,784,000	534,733,000
1989	562,258,000 7/	546,902,000 8/	565,908,000	559,538,000
1990	577,235,000 9/	590,276,000	593,497,000	589,594,000 10/
1990 Sequester				-8,117,000
1991	605,349,000	613,686,000 11/	626,986,000	615,272,000 12/
1991 Sequester				-8,000
1992	658,557,000	667,820,000	652,861,000	659,538,000 13/
1993	699,809,000	688,633,000	688,633,000	681,342,000 14/
1994	677,135,000	716,054,000	716,054,000	716,054,000
1995	731,500,000 15/			

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions.

2/ Excludes $19,135,000 in NRSA training programs not considered.

3/ Excludes $19,135,000 in NRSA training programs not considered.

4/ Amounts shown reflect the sequestered amount of $24,482,000.

5/ Excludes $26,730,000 in NRSA training programs not considered.

6/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

7/ The 1989 Request excludes funds for AIDS research and education ($3,650,000) that has been proposed for consolidation at the Office of the Assistant Secretary for Health.

8/ Exludes $25,509,000 in NRSA training programs not considered.

9/ The 1990 Request excludes funds for National HIV program ($5,394,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

10/ Excludes enacted administrative reduction of $2,293,000.

11/ Excludes $23,872,000 in NRSA training programs not considered.
12/ Excludes enacted administrative reductions of $15,238,000 and $1,762,000.
13/ Excludes enacted administrative reductions of $435,000 and $4,107,000.
14/ Excludes enacted administrative reductions of $7,291,000.
15/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Diabetes, endocrinology and metabolism...		263,127		274,326		275,865		289,619		300,953		11,334
Digestive diseases and nutrition....		121,623		128,606		137,959		145,432		151,129		5,697
Kidney disease, urology and hematology.......		128,694		147,282		153,743		164,319		170,757		6,438
Subtotal, Extramural.		513,444		550,214		567,567		599,370		622,839		23,469
Intramural research..	438	74,233	457	79,592	460	82,449	480	81,841	462	83,431	-18	1,590
Research management and support........	165	21,295	172	24,468	178	24,052	180	24,405	180	25,230	---	825
Subtotal, obligations......	603	608,972	629	654,274	638	674,068	660	705,616	642	731,500	-18	25,884
Unobligated Balance Lapsing............		728		619		158		---		---		---
Total, Budget Authority........		609,700		654,893		674,226		705,616		731,500	-18	25,884

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
638	$674,226,000	660	$705,616,000	642	$731,500,000	-18	+$25,884,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute of Diabetes and Digestive and Kidney Diseases conducts and supports basic and clinical research related to many serious and costly diseases affecting the public health. These include but are not limited to: diabetes mellitus; endocrine diseases including osteoporosis; metabolic diseases including cystic fibrosis; digestive diseases including those of the liver and biliary tract, pancreas, and gastrointestinal tract; nutrition and eating disorders including obesity; kidney failure; genitourinary diseases; and diseases of the blood-forming organs. Several of these diseases are among the leading causes of disability and death; all seriously affect the quality of life of those who have them. Each year, their economic burden exceeds $300 billion.

The NIDDK's programs are closely linked by common fundamental biological questions. The Institute places a high priority on research that explores those questions, and on transferring the promising results of basic research to clinical research on preventing and treating disease. This year, several findings from basic research begun over the past two decades have resulted in clinical results that are likely to help prevent disease and improve public health.

The results of two NIDDK-sponsored clinical trials focusing on preventing or delaying the complications of insulin-dependent diabetes mellitus (IDDM) were announced this year. Researchers from both studies believe that the results will also apply to individuals with non-insulin-dependent diabetes mellitus and lead to changes in the medical management of patients with either type of diabetes. The "Diabetes Control and Complications Trial" (DCCT), which included more than 1,400 participants, showed that very strict control of blood sugar levels can dramatically reduce major complications of this disease, including eye and kidney damage, foot ulcers, and amputations. Because strict control of blood sugar level is difficult by currently available methods, these results also underscore the significance of research efforts to develop systems of automatic insulin treatment in response to constant blood sugar monitoring. Noninvasive methods to monitor blood sugar and efforts to genetically engineer insulin-producing cells are two avenues of research that may lead to better management of blood sugar levels. The results of another trial in more than 400 patients with IDDM showed that a commonly prescribed medication for hypertension and heart failure significantly slowed the progression of kidney disease in these individuals. These results have the immediate potential of saving lives, improving quality of life, and reducing health care costs. The annual Medicare cost for treating end-stage renal disease (ESRD) either by dialysis or kidney transplantation is currently approximately $7.2 billion. The most common diagnosis in the ESRD population is kidney disease of diabetes mellitus.

New knowledge about the bacterium Helicobacter pylori will provide the basis for designing methods to diagnose, monitor, treat, and prevent infection with this organism, which has been determined a major cause of peptic ulcer disease. NIDDK-sponsored research on the association of H. pylori with ulcer and the continuing studies to better understand it are likely to result in significant health care cost savings. As documented in a one-year follow-up study, eradication of H. pylori prevents recurrence of ulcer disease in the majority of patients, a finding that could lead to an estimated $760 million annual saving in health care costs.

Other ongoing or newly initiated clinical studies focusing on prevention or delay of disease include primary prevention studies for non-insulin-dependent and insulin-dependent diabetes mellitus, the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, studies of new devices for clearing mucus in the lungs of cystic fibrosis patients, studies of wasting in AIDS, a major initiative in obesity research that includes the establishment of a National Task Force on Prevention and Treatment of Obesity, a trans-NIH initiative, under NIDDK leadership, in bionutrition, a pilot clinical study on reduction of morbidity and mortality among hemodialysis patients, a trial looking at ways to reduce hypertension-associated kidney disease in African Americans, and a trial on the treatment of benign prostatic hyperplasia.

Underpinning the clinical studies supported by the NIDDK are many advances in fundamental research. This year, significant advances in basic research reported by NIDDK grantees and investigators included progress in identifying genes associated with diabetes, use of recombinant adenovirus to introduce healthy genes into pancreatic cells, the finding that parathyroid hormone has a strengthening effect on a certain type of bone while weakening another type, development of an animal model in which aspects of gene therapy for cystic fibrosis can be addressed, initial success in gene therapy for Duchenne muscular dystrophy in an animal model, development of a "Tay Sachs" mouse for research, discovery of a novel family of small proteins that may be useful in treating inflammatory bowel disease, advances in knowledge about tolerance for organ transplants, discovery of a possible beneficial role for "brown fat" in obesity in rodents, advances in understanding how the body increases zinc uptake for certain cell processes, identification of a protein resembling nerve growth factor that is specific for the male genitourinary system and appears to mediate growth of prostate cells, discovery of an underlying mechanism of antidepressant action, and development of an analytical system to determine if residual cancer cells remain in the bone marrow of patients with chronic myelogenous leukemia after bone marrow transplantation.

The President's appropriation request of $731,500,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Diabetes and Digestive and Kidney Diseases during the last five years has been as follows:

	Amount	FTE
FY 1990	$574,916,000	599
FY 1991	609,700,000	603
FY 1992	654,893,000	629
FY 1993	674,226,000	638
FY 1994	705,616,000	660

Purpose and Method of Operation

The major program areas of the Institute foster basic, clinical, and applied and developmental research through investigator-initiated research grants, program project grants, research center grant awards, research career development awards, Small Business Innovation Research awards, research and development contracts, and intramural research. Training for research careers and/or teaching is accomplished through National Research Service Awards. NIDDK-supported information clearinghouses distributed more than 300,000 documents last year to professionals, patients, and the public about the diseases within the Institute's mission.

Overall Budget Policy

The FY 1995 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases provides a 3.7% percent increase and totals $731,500,000, an increase of $25,884,000 over the FY 1994 level.

In FY 1995, the request will support 1,928 research project grants as compared to 2,055 in FY 1994. The noncompeting research project grants request for the NIDDK shows an increase from an average of $220,673 in 1994 to an average of $251,673 in 1995, a one-time increase of 13.9 percent. The two largest clinical trials of the institute, the Diabetes Control and Complications Trial and the Modification of Diet and Renal Disease Trial, are being completed in 1993 and 1994. Their replacement trials, to be conducted through cooperative agreements for clinical trials, and their convergence in the same competing year causes this large change in the noncompeting average size. On the other hand, the combined effect on earlier noncompeting average size as the two earlier trials finished was to reduce the growth in noncompeting average size between 1992 and 1993 to 1 percent, and between 1993 and 1994 to 0 percent. All ongoing grants of the NIDDK are held to a four percent increase, in accordance with the NIH Cost Management Plan. The NIDDK has elected to fund an additional 93 grants in the FY 1995 rather than increasing the average cost of competing grants.

The FY 1995 request includes funding for 61 research centers, 213 research career awards, 64 other research grants, 868 research trainees, and 42 R&D contracts.

The FY 1995 requests for Intramural Research and Research Management and Support are net increases. They provide for built-in mandatory increases such as centrally furnished services and for annualization of the 1994 pay raises, offset by savings from administrative cost and staffing reductions (18 FTEs).

Extramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$567,725,000	$599,370,000	$622,839,000	+$23,469,000

Funding for the Extramural Program during the last five years has been as follows:

	Amount
FY 1990	$483,825,000
FY 1991	513,846,000
FY 1992	550,770,000
FY 1993	567,725,000
FY 1994	599,370,000

Diabetes, Endocrinology, and Metabolic Diseases

The NIDDK's Diabetes, Endocrinology, and Metabolic Diseases program has primary responsibility at the National Institutes of Health for extramural research and research training in endocrinology and metabolism, with special emphasis on diabetes, cystic fibrosis, and other diseases and disorders encompassed by these disciplines.

Rationale for Budget Request

The FY 1995 budget request for the Extramural Program is $622,839,000, an increase of 3.9 percent over the FY 1994 estimate of $599,370,000. With the FY 1995 extramural request these funds will provide support for the following activities: Diabetes, Endocrinology, and Metabolic Diseases, $300,953,000, an increase of $11,334,000 or 3.9% over the FY 1994 estimate of $289,619,000; Digestive Diseases and Nutrition, $151,129,000, an increase of $5,697,000 or 3.9% over the FY 1994 estimate of $151,129,000; Kidney, Urologic, and Hematologic Diseases, $170,757,000, an increase of $6,438,000 or 3.9% over the FY 1994 estimate of $164,319,000.

Diabetes

The NIDDK is the lead agency of the Federal government for research efforts to combat diabetes mellitus and its complications. Diabetes is the sixth leading cause of death from disease in the U.S., afflicting an estimated 13 to 14 million people, but approximately one-half of these cases are undiagnosed. It is also the leading cause of new adult blindness, kidney failure, and non-traumatic amputation, and is a major risk factor for stroke, heart attack, and premature death. The annual economic cost to the nation of diabetes is estimated to be over $90 billion in medical care and lost productivity. In addition, minority populations, including African Americans, Hispanics, Native Americans, Hawaiians, and Alaska Natives, are disproportionately affected by diabetes and by its enormous cost burden.

Insulin-Dependent Diabetes Mellitus (IDDM): Approximately 500,000 to 750,000 Americans have IDDM. Most of these people are children or young adults. IDDM occurs when a person's immune system mistakenly attacks and destroys the insulin-producing beta cells of the pancreas. Eventually, these individuals require insulin from an external source in order to regulate their blood glucose level and thus survive.

Results announced in June 1993 of a 10-year landmark clinical trial supported by the NIDDK indicate that very carefully controlled blood glucose levels dramatically reduce the risk of life-threatening complications due to diabetes. Complications of diabetes include retinopathy (eye damage), nephropathy (kidney damage), and neuropathy (nerve damage) leading to gangrene followed by lower extremity amputation. The Diabetes Control and Complications Trial (DCCT), the most comprehensive clinical trial in the history of diabetes research, determined that, compared to traditional insulin therapy, intensive treatment (1) reduced the incidence of retinopathy (the leading cause of blindness in adults) by 76 percent; (2) prevented or delayed progression of nephropathy by 35 to 56 percent; and (3) reduced the incidence of foot ulcers and amputations by 60 percent. In addition, because the development of complications is similar in insulin-dependent and non-insulin-dependent diabetes, the NIDDK believes that the recommendations for tight blood glucose control, and diabetes management in general, apply to both forms of the disease. The NIDDK is now working with the Centers for Disease Control and voluntary and professional organizations and industry to promulgate the results and recommendations of the DCCT. The DCCT is being recognized as the most important clinical trial to date in the history of diabetes research.

In another exciting area of diabetes research, scientists are hopeful that new findings may lead directly to a therapy for humans that might delay the onset of the disease or prevent it all together. Two research groups recently discovered a means of preventing IDDM in animals. Using a mouse model of IDDM that closely parallels the human disease, researchers have now discovered the probable cause of the attack on the pancreas cells. The pancreas cells contain on their surface a protein (called GAD) that closely resembles a protein found in a common virus that causes colds, sore throats, and sometimes more serious symptoms. Researchers believe that, after attacking the virus following an infection, the immune system is fooled into attacking the pancreas cells because of the GAD protein on their surface. Both groups reported that injection of the GAD protein directly into the mice subsequently prevented the immune system from attacking the pancreas cells and thus prevented the development of IDDM.

Non-Insulin-Dependent Diabetes Mellitus (NIDDM): Treatments for NIDDM can only come from a comprehensive understanding of the process that leads to the disease. Thus, the NIDDK continues to be very supportive of research on the genetic, metabolic, and environmental risk factors that result in NIDDM. For example, recent studies have uncovered clues to understanding the changes in the body's response to insulin that cause NIDDM. Observations include the ascertainment of functionally different forms of the cellular receptor for insulin, and the identification of the biochemical steps linking the insulin receptor to its response systems inside the cell. Even a slight alteration in one of the many components of the insulin processing mechanism can cause the body to become resistant to the effect of insulin, which results in NIDDM. The exciting basic knowledge being obtained on the insulin response pathways in normal cells is quickly being applied to a better understanding of insulin resistance in NIDDM.

Diet has long been associated with NIDDM. Recent studies have shown that intake of fat, fiber, sugar, and other components of the diet is related to risk of diabetes. Another environmental variable is physical activity; exercise alone cuts the risk of NIDDM to about one half the level seen without activity. In addition, smokers have a higher risk of diabetes, as do women who use oral contraceptives.

Of great concern is the extremely high risk for NIDDM among Native Americans. The long-term effects on offspring of mothers having abnormal glucose processing during pregnancy were examined in Pima Indians between the ages of five and 24. Indicators of impending NIDDM were observed at an earlier age in offspring of women with abnormal glucose tolerance during pregnancy, and these children were more obese and had higher rates of abnormal glucose processing themselves.

Diabetes Genes: Genetics appears to be the common denominator underlying the various factors that lead to diabetes. Intensified genetics research offers great promise for understanding, controlling, and preventing diabetes. The NIDDK will continue to enhance support for both the basic understanding of diabetes and for the direct application of this knowledge to population screening and gene therapy.

NIDDM is caused by genetic factors that affect both insulin production by the pancreas and insulin action in insulin-responsive tissues, such as muscle, fat, and liver. The tendency for NIDDM to occur in family members has been known for some time. Within the last few years, considerable evidence has accumulated that NIDDM in families is due to an inherited defect in genes that predispose individuals to this disease. Further evidence that differences in genetic susceptibility exist in NIDDM has been obtained from examination of a relatively rare sub-group of this disease, referred to as maturity-onset-diabetes of the young (MODY), in which there is a clear transmission through several generations. Genetic studies of families with this type of diabetes have shown a close correlation between a particular portion of the glucokinase gene and the disease itself. The gene in question is important in the metabolism of glucose. In similar genetic studies, genetic analyses of Pima Indians have provided evidence for a gene that may be important in the development of the disease. This is the first example of how a genetic mutation in a key regulatory enzyme of glucose metabolism can cause diabetes. Continued application of genetic approaches may guide researchers to particular areas of the human genome in their quest to ascertain other genes responsible for NIDDM.

Identification of genetic variants that predispose people to or protect them from IDDM are extremely useful. Combining genetic screening with immunological marker analyses will strengthen our ability to recognize individuals at high risk for the development IDDM. This will be especially important as we progress into the screening of specific populations at-risk individuals who are not first-degree relatives of IDDM patients. The NIDDK is in the process of testing methods to prevent people at risk for IDDM from developing the disease.

Gene Therapy: Recent progress in gene therapy research holds promise for the treatment of diabetes, and the NIDDK continues to encourage the development and application of gene therapy approaches in this area. The use of recombinant adenovirus vectors for high-efficiency gene transfer of a marker gene into the insulin-producing beta cells of the pancreas is a new application of molecular biological technologies to diabetes research. Using this marker, it is possible to monitor whether the gene has gotten to the right place in the body, and whether it remains in place and active. Recombinant adenovirus vectors have been shown to be an efficient means of introducing genes into beta cells in tissue culture.

Diabetes in Minority Populations: Research has shown that the most prominent risk factors for NIDDM are a family history of diabetes, obesity, insulin resistance, hyperinsulinemia, a history of gestational diabetes, and impaired glucose tolerance. African-Americans, Hispanic-Americans and Native Americans are disproportionately affected. The U.S. Congress, the Department of Health and Human Services and the National Diabetes Advisory Board have highlighted the growing problem of diabetes in minority populations as important public health issues deserving increased research effort.

As part of its continuing commitment to address this need, the NIDDK will initiate in FY 1994 a major clinical trial of preventive intervention strategies, targeted at individuals with impaired glucose tolerance, a history of gestational diabetes, and/or newly diagnosed NIDDM. Minorities will make up 50 percent of the study population. Interventions may include diet, exercise, and pharmacologic agents. The number and types of interventions tested will depend on the funds available. This new initiative is a collaboration between the NIDDK, the NIH Office of Research on Minority Health, and the National Institute of Child Health and Human Development.

Another component of the NIDDK's diabetes prevention effort in minority populations will build on the Institute's successful program of diabetes prevention studies in Alaskan Natives and Native Americans, and will target prevention of diabetes and complications in other minority populations.

Clinical Trials: With the completion of the NIDDK-supported Diabetes Control and Complications clinical trial, the Institute is initiating a major clinical trial of preventive intervention strategies among people with impaired glucose tolerance or gestational diabetes mellitus who are at high risk for the development of NIDDM. This type of diabetes has disproportionate impact in minority populations, and these population segments will be overrepresented among the trial participants in order to insure applicability of the results to these groups. Several different non-pharmacologic and pharmacologic interventions will be considered for inclusion in the trial.

In FY 1994, the NIDDK also initiated a new clinical trial for the prevention of IDDM. This trial will test whether intervention during the time prior to onset of IDDM can delay the clinical appearance of the disease. At-risk individuals will be identified and, since IDDM is considered an autoimmune disease, attempts made to "immunize" them against self destruction of their insulin-secreting pancreas cells, which otherwise would result in IDDM.

Endocrinology

Osteoporosis and Related Bone Disorders: As a major participant in osteoporosis and related bone disorders research at the NIH, the NIDDK continues to strongly encourage and support investigations that are vital to the health of America's aged population. Most recently, as the result of a program initiative, the Institute funded ten new grants to study hormonal regulation of bone in health and disease. These projects will expand knowledge on the effect of systemic hormones, local growth factors, and cytokines in the maintenance of bone density and the regulation of bone turnover. For example, primary hyperparathyroidism is a disorder of mineral metabolism characterized by mildly elevated levels of parathyroid hormone (PTH) and mild hypercalcemia. This can have devastating long-term effects on bone, since one of the overall functions of PTH is to transfer calcium from blood to bone. Previous research had shown that at other times PTH can also cause increases in bone mineral density. NIDDK investigators now have shown that while excessive PTH adversely affects cortical bone, for example vertebra, it can have a beneficial effect of the preservation of cancellous bone (e.g. femur). These findings may have a bearing on the proposed use of controlled PTH administration in combination with other hormones to osteoporotic patients to preserve cancellous bone.

The menopause, particularly at an early age, with its resultant decrease in estrogen levels, places women at increased risk for osteoporosis and resulting bone fractures. In postmenopausal women, estrogen replacement is effectively preventing osteoporosis. The NIDDK currently is participating in a comprehensive evaluation of the effects of postmenopausal estrogen replacement on lipids, blood coagulation, glucose metabolism, blood pressure, and bone mass. This study, the Postmenopausal Estrogen/Progestin Intervention (PEPI) clinical trial, involving four other NIH institutes, compares the risks and benefits of several approaches to estrogen replacement to prevent osteoporosis.

Hormones and Cancer: The ability of cells to regularly undergo cell division involves a complex series of events mediated by the expression, often in a hormone- dependent fashion, of key proteins which regulate whether the cell remains in a quiescent stage or progresses to a stage of the cell cycle which leads to cell division. Now it appears that a cyclin is expressed at a different stage in the cell cycle, with a different role in progression of the cell to cell division. This protein has been mapped to a particular chromosome and has been implicated in several human tumors. It appears to be another factor whose expression is regulated by hormones and by growth factors and whose inappropriate expression may play a role in the development of human cancers.

Metabolic Diseases

Cystic Fibrosis: As the lead Institute for cystic fibrosis research at the NIH, the NIDDK continues its commitment to foster progress in combating this devastating disease of children and young adults. In 1993 and 1994 the Institute funded the first three NIH research centers for gene therapy of cystic fibrosis and other genetic diseases. In addition, since most patients suffer nutritional problems and disorders, the Institute initiated a program to encourage development and testing of interventions to improve nutritional status, growth, and development in cystic fibrosis.

Chronic pulmonary infection is the major cause of morbidity and mortality in cystic fibrosis. Aminoglycoside antibiotics are generally used to treat the organisms responsible for the infection. In a randomized, cross-over design study, the aminoglycoside antibiotic tobramycin was administered by aerosol for four weeks and compared to a placebo. There was a ten-fold decrease in the density of the infecting bacterium in the sputum. There was also a decrease in the need for other antibiotics to treat infection during the aerosol therapy.

A new hand-held device has been developed which enhances mucus clearance in cystic fibrosis. Exhalation through this devices cause oscillations of airflow which vibrate the airway walls to loosen mucus. It also promotes movement of mucus by decreasing the collapsibility of the airways and accelerating airflow. The amount of mucus produced after 15 minutes use of the device was compared to the same durations of vigorous voluntary coughing and chest physical therapy in 18 cystic fibrosis patients with mild to moderately severe lung disease. User of the devices resulted in three times the sputum production seen with either voluntary cough or chest physical therapy.

Since the cloning of the gene responsible for cystic fibrosis, development of safe and effective methods of gene therapy has become a major goal of cystic fibrosis research. An animal model in which the safety and efficacy of gene therapy could be tested would facilitate progress. A rodent model of cystic fibrosis has recently been developed but its value is limited by the differences in the structure and function of human and rodent lung. Liposomes have been used to deliver the cystic fibrosis gene to mice both intravenously through the tail vein and directly to the lung with aerosolized delivery.

These results provide a number of promising approaches to gene therapy for cystic fibrosis. Target cells for gene therapy are being defined to ameliorate both lung and liver disease. Stable expression of the cystic fibrosis gene have been achieved with a variety of factors. Model systems have been developed to evaluate and compare promising vectors for efficacy and safety.

Duchenne Muscular Dystrophy: NIDDK-supported researchers have exploited a mouse model of Duchenne's muscular dystrophy to explore the use of gene therapy to cure this disease. The scientists used a special line of inbred mice that carries a damaged version of the gene responsible for the disease. A shortened, and more manageable version, of the healthy gene was inserted into early mouse embryos. The resulting mice did not express the disease. This exciting result opens up the possibility of treating the human disease at some point in the future. This exciting result opens up the possibility of treating the human disease at some point in the future.

Digestive Diseases and Nutrition

The NIDDK's Digestive Diseases and Nutrition program has primary responsibility at the National Institutes of Health for extramural research and research training in digestive diseases and nutrition.

Digestive Diseases

The social and economic impact of digestive diseases is enormous with disorders of the digestive tract ranking among the leading causes of hospitalization, surgery, and disability in the U.S. Twenty million Americans are treated for a chronic digestive disease each year. An estimated 200,000 people miss work each day because of digestive problems, resulting in current costs of approximately $70 billion a year in lost wages, reduced productivity, health care expenditures, and disability payments. NIDDK supports basic and clinical biomedical research and research training in the normal function and diseases of the gastrointestinal tract and associated organs.

Inflammatory Bowel Disease: The NIDDK will encourage expanded research on a unique family of peptides just recently discovered. These novel intestinal proteins promote healing after injury of the intestinal tract surface, a condition found in inflammatory bowel disease. This digestive disease includes both Crohn's disease and ulcerative colitis and is characterized by inflammation or ulceration of the small and large intestine. A number of observations have been obtained in initial characterization of these proteins. They underscore the importance of this finding and highlight distinctive features of these unique peptides, which are important throughout the gastrointestinal tract.

Ulcers: NIDDK will continue to pursue studies to understand the importance of the bacterium _H. pylori_ in the natural history of peptic ulcer disease. Effective treatment could result in significant health care cost savings and particularly benefit minorities and those of low socioeconomic status who are disproportionately affected by ulcer disease. Over the last five years, rapidly accumulating data have shown that _H. pylori_ is a major causative factor in peptic ulcer disease. Several studies have shown that more than 90 percent of patients with duodenal ulcers and 70 percent of patients with gastric ulcers are infected with the organism. Chronic infection with _H. pylori_ has also been linked to stomach cancer. New knowledge about the basic biology of this bacterium is important in designing strategies to diagnose, monitor, treat and prevent this infection.

Liver-Assist Devices: The Institute will seek studies to perfect an artificial liver that will tide a patient over until his own liver recovers or until a suitable donor can be located. When the liver fails, death results promptly. Liver transplants can prove life-saving, but the treatment is expensive. Also, it is often difficult to locate appropriate livers in an emergency. This work is in its infancy, but already has helped save the life of a 12-year old girl with what would have been fatal hepatitis.

Liver-assist devices, developed using animal models, have been studied in only very few humans to date. One uses liver cells from pigs, harvested and then cryopreserved. In studies in animals with acute, terminal liver insufficiency, beneficial metabolic effects were noted. In one clinical case study, a 33-year old male patient with alcohol-induced cirrhosis was treated for six hours with the device. He was an unsuitable candidate for liver transplantation and was in coma within 48 hours of admission. Within two hours after initiation of treatment, his mental status improved and, at the end of treatment, his plasma ammonia was reduced substantially. During the subsequent three weeks, the patient's liver function and mental status gradually improved, and he entered an alcohol treatment program. He will now be eligible for liver transplantation. Thus, the device afforded a bridge to transplantation.

Researchers will continue to explore mixed immunologic tolerance, which if better understood and induced, would usher in a new era of tissue and organ transplantation. Surgeons were able to transplant organs before really understanding the immunology of the procedure. Once the transplant had passed through a rejection crisis, sometimes only small amounts of immunosuppressants were required. There were even instances when it was possible to discontinue immunosuppression altogether, i.e., tolerance had occurred.

Recent observations have demonstrated that transplantation of a liver may have a beneficial effect on metabolic diseases in which not only the liver, but other tissues, are diseased. Encouraging clinical observations have been made involving the migration of cells from the transplanted organ to the organ recipient. These observations suggest the possibility of induced tolerance to transplanted organs. Progress along these lines might simultaneously reduce the inconvenience and risk associated with lifelong dependence on immunosuppressants. Induced tolerance to graft transplants would both improve the quality of life of the patient and reduce the cost of the procedure.

Nutrition

NIDDK fosters and supports research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged to increase our knowledge of the function and requirements of nutrients, the relationship of diet and nutrients to health and disease, and the prevention and treatment of diseases as an outgrowth of nutrition research. Clinical problems of interest to NIDDK include obesity, anorexia nervosa, diabetes, chronic renal disease, end-stage liver disease, gastrointestinal dysfunction, bone disease, total parenteral nutrition, and combined nutrient-drug interactions and management of patients.

Bionutrition: As the lead institute at NIH for nutrition research, the NIDDK supports an extensive portfolio of research on nutrient metabolism and other fundamental research in the nutrition sciences. Consistent with this leadership role, the NIDDK has become the organizational locus for the Division of Nutrition Coordination, including the NIH Nutrition Coordinating Committee. The NIDDK will also provide leadership for a trans-NIH initiative in bionutrition. The NIDDK intends to convene a working group of Nutrition Coordinating Committee representatives from the institutes with major nutrition research portfolios to determine the most appropriate areas of focus for a trans-NIH solicitation in bionutrition. These efforts will be augmented by the assistance of an ad hoc group of external advisors. This will allow the development of a trans-NIH consensus about the future direction of nutrition research, and the bionutrition initiative will be a specific first step. One goal will be to establish a trans-NIH Nutrition Research Training Program, which will involve a dialogue on nutrition training that will include both intramural and extramural components. The effort will be responsive to the training recommendations of the Institute of Medicine's report, "Opportunities in the Nutrition and Food Sciences."

Nutrient Metabolism: Future research will focus on understanding the absorption, metabolism, and functions of zinc in normal and disease processes. Clinical studies have clearly shown that several disease states drastically alter zinc metabolism. Early experiments revealed that zinc induced the synthesis of a zinc binding protein, a discovery that laid the groundwork for studies on regulation of genes in transgenic animals by dietary zinc. NIDDK-supported research now has shown that expression of this zinc binding protein provides a mechanism for cells to augment zinc uptake for zinc-dependent cellular processes. Hormonal regulation of zinc metabolism mobilizes a redistribution of zinc in a tissue-specific fashion, which suggests that this nutrient is important in trauma and infection and in immunologic rejection of tissue transplants. Once the mechanism that controls for intestinal zinc transport fails, the host defense is diminished by decreased immune function and decreased gene regulation and may lead to an unsatisfactory clinical outcome. The finding that expression of this protein in bone marrow was dependent on dietary zinc intake also led to establishing a biomarker for zinc status assessment in humans.

Obesity: Obesity is a significant public health problem in the United States. Prevention of obesity would delay the onset or slow the progression of diabetes, hypertension, heart disease, and some forms of cancer. These efforts could potentially yield $50 billion dollars yearly in health care savings. The Institute plans to continue the work of a major initiative in obesity which it has undertaken. A National Task Force on Prevention and Treatment of Obesity has been established; development of an Obesity Resource Information Center is currently in progress; and three new obesity/nutrition centers were funded, which complement an already existing obesity center and five Clinical Nutrition Research Units (CNRUs). An animal model core was also funded at an NIDDK-supported CNRU. As part of its obesity initiative, the NIDDK and/or the Task Force have cosponsored workshops on the pharmacologic treatment of obesity; physical activity and obesity; central obesity, insulin resistance and coronary artery disease; obesity treatment; and prevention of obesity. Fact sheets produced or in preparation by the NIDDK Obesity Resource Information Center, with the advice of the Task Force, address binge eating disorder; dieting and gallstones; choosing a safe and sensible weight loss program; understanding adult obesity; obesity in minorities; weight cycling; and childhood obesity. The Task Force also published a major paper on very low calorie diets and is working on a position paper on weight cycling.

Underpinning these efforts is the NIDDK's extensive research portfolio of basic and clinical research. NIDDK-sponsored research will seek to promote studies of the molecular pathogenesis of obesity, including the search for the genes involved in obesity-susceptibility. Physiological studies in animals and humans indicate that body fat content is regulated by interlocking control systems that affect both food intake and energy expenditure.

Researchers supported by the NIDDK have prepared detailed molecular genetic "maps" in the regions of five rodent mutations which result in obesity. These maps are made by identifying unique DNA sequences near the obesity mutations. The location of these sequences relative to the mutations is determined using carefully designed mating schemes between large numbers of animals. Experiments are now under way to see whether these genes play a role in the obesity of Caucasians, African-Americans, Native Americans and Hispanics. A similar strategy is being used to identify rodent genes that convey susceptibility to non-insulin-dependent diabetes mellitus (NIDDM) in obese individuals. Over 80 percent of patients with NIDDM are obese, and their diabetes is generally greatly improved by modest weight loss.

The recent molecular mapping of a particular rat mutation has opened up the possibility of examining the molecular physiology in these animals before they become obese. Changes have been detected within the first few days of life -- in brain and pancreatic systems critical to the control of energy balance. This model can be used both to understand the underlying causes of obesity and to test a variety of potential treatments.

Many other studies of obesity are gaining new insights through the use of animal models. Brown adipose tissue is a special sort of fat important in maintaining body temperature. Researchers studying obesity have created transgenic mice which lack this specialized tissue. Investigators have used transgenic technology to create lines of transgenic mice that have a primary deficiency of brown adipose tissue. An exciting finding is that the mice with reduced amounts of this tissue, commonly called "brown fat," have severe obesity. In one strain of animals in which the deficiency of the "brown fat" is persistent through life, the obesity is progressive and is as severe as seen in any model of obesity. In the other strain, "brown fat" regenerates later in life, and as this occurs, obesity reverses. These results suggest that, at least in rodents, "brown fat" plays a significant role in obesity.

Kidney, Urologic, and Hematologic Diseases

The NIDDK's Kidney, Urologic, and Hematologic Diseases program has primary responsibility at the National Institutes of Health for extramural research and research training in kidney, urologic, and fundamental aspects of hematologic diseases.

Kidney Diseases

The number of people who completely lose kidney function has increased at an annual rate of about 10 percent during the last decade. Survival for patients with permanent kidney failure, called end-stage renal disease (ESRD), requires either dialysis therapy or kidney transplantation. The annual mortality rate among hemodialysis patients in the U.S. exceeds 20% and is one of the highest rates among industrialized countries. Thus, the NIDDK has initiated a multicenter clinical trial to improve morbidity and mortality among this patient population. It is called the "Reduction of Morbidity and Mortality Among Hemodialysis Patients."

The most common cause of ESRD is the kidney disease of diabetes mellitus (KDDM). In a recent breakthrough, researchers have shown that a drug that controls high blood pressure can greatly slow the progression in diabetics of the onset of kidney failure. Previous animal studies offered hope the drug might help humans, but a study this year reported the first clinical confirmation of a benefit to diabetes patients. Researchers believe the data show that the drug can postpone kidney failure by a decade or more.

Kidney disease associated with hypertension is the most common diagnosis among African Americans with ESRD. The primary goal of the NIDDK-supported African American Study of Kidney Disease and Hypertension (AASK) is to determine whether one of two levels of blood pressure control and one or more classes of antihypertensive medications are more effective in slowing down the loss of kidney function among African American men and women with kidney disease associated with hypertension. The pilot study has more limited objectives involving the testing of procedures for recruitment, treatment and compliance to the antihypertensive medications, study procedures, and clinic visit schedule. To capitalize on the AASK, the NIH Office of Research on Minority Health has provided support to the NIDDK for a study of barriers to participation in clinical trials and compliance to medical regimens among African Americans.

Other leading causes of ESRD are glomerulonephritis, including IgA nephropathy, and cystic kidney disease, such as autosomal dominant polycystic kidney disease. Initiatives within the NIDDK have supported and will continue to encourage research on these diseases.

Urologic Diseases

Investigators are continuing research on the role of interactions between smooth muscle cells and glandular cells in the regulation of the growth and development of the prostate and are identifying exogenous growth factors which stimulate proliferation of cells of the prostate. Investigators have demonstrated that these discrete cell types secrete a substance into the media in which they are being grown. They have shown that this substance has an effect of the growth of other cells types. The specific substance secreted, however, has not yet been characterized. Nor have the specific sites of secretion or the receptors for this substance been identified. Recently, NIDDK researchers have identified a protein resembling nerve growth factor. It appears to mediate the growth of prostate cells and to be specific for the male genitourinary system.

If total relief of symptoms of benign prostatic hyperplasia is to occur, pharmacological interventions must be developed which either block or reverse the response of the bladder to obstruction of the outlet. Additional studies must be directed at correlating the genetic response of the bladder with that of the enlarging prostate. This might lead to an understanding of the factors that affect specific gene sequences in both organs. A recently initiated clinical trial on the treatment of benign prostate hyperplasia may provide clinically important results.

Diseases and disorders of the urinary tract are a major health problem for women of all ages. Urinary tract infections, urinary incontinence, and interstitial cystitis are major disabling disorders, which result in a significant number of physician visits and hospitalizations and which result in untold health care expenditures. The pathogenesis of many these disorders remains poorly understood, and preventive and curative methods have yet to be developed. The NIDDK continues to issue Requests for Applications in these areas to encourage increased basic and clinical research on women's urologic health. The NIDDK-supported Interstitial Cystitis Data Base began patient recruitment this year. A recently reported NIDDK-supported study showed that intravaginal administration of estriol could prevent recurrent urinary tract in infections in postmenopausal women.

Kidney and Urologic Research Centers

The George M. O'Brien Kidney and Urological Research Centers Program supports interdisciplinary investigations that address the basic, clinical, and applied aspects of biomedical research in renal physiology and pathophysiology, nephrology, and urology. Areas of specific research emphasis include chronic kidney disease, renal injury, congenital kidney disorders, glomerulosclerosis, urinary tract stone disease, and mechanisms of prostate growth. In FY 1993, two additional kidney centers and three additional urology centers were funded. The new urology centers are supported by both the NIDDK and the National Cancer Institute and will focus on prostate growth, both benign and malignant. The NIDDK now supports a total 12 George M. O'Brien Kidney and Urological Research Centers. In addition, the NIDDK supports two Research Centers of Excellence in Pediatric Nephrology and Urology.

Hematologic Diseases

The primary emphasis of the NIDDK Hematology program is a broad approach to understanding the fundamental processes underlying the normal and pathologic function of blood cells and the blood forming system. Major areas of interest include hemoglobin; acquired and inherited anemias; membranes; iron metabolism and storage; formation of the blood in the bone marrow; immunohematology; bone marrow biology; and the application of the fundamental knowledge gained to such current issues as gene transfer therapy. For example, as a part of the NIDDK's basic studies on hemoglobin, understanding of the genetic basis of Cooley's anemia and sickle cell disease has been advanced considerably. In addition, advances are being made in achieving a basic understanding of the processes leading to a large number of other hematologic disorders that might lend themselves to gene therapy. Among these are diseases of iron transport and storage, such as hemochromatosis, the red blood cell membrane disorders, including hereditary spherocytosis, the porphyrias, and hemophilia.

Work continues on the development of drugs for sickle cell disease and Cooley's anemia, and on the development of oral iron chelator drugs for Cooley's anemia patients. In another area, this year, NIDDK-supported researchers reported the development of a sensitive analytical system to determine if residual cancer cells remain in the bone marrow of patients with chronic myelogenous leukemia (CML) after bone marrow transplantation. This assay will be a useful prognostic tool in the management of CML patients. The molecular lesion that causes hereditary elliptocytosis was discovered. This mechanism, which involves alternative splicing of messenger RNA, may also apply to other diseases.

During the past two decades, major advances have been made in understanding the molecular basis for inherited diseases. The clinical and biochemical effects of diseases have been clarified, and, for an ever-increasing number of genetic disorders, the molecular defects have been described. Hematologists have been leaders in exploiting the techniques of molecular biology that have enabled researchers to introduce healthy genes into the DNA of individuals with gene defects. In FY 1993, the NIDDK began to support the planning of molecular hematology research centers to develop methods of characterizing, identifying, treating, and curing inherited diseases of the blood. The Institute hopes to begin supporting three such Centers in FY 1994.

Intramural Research

Authorizing Legislation: Sections 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	
460	$82,449,000	480	$81,841,000	462	$83,431,000	-18	+$1,590,000

Nearly 250 research activities are under way in the NIDDK intramural research program at facilities in Bethesda, Maryland, and Phoenix, Arizona.

Funding for the Intramural Research program during the last five years has been as follows:

	Amount	FTEs
FY 1990	$68,425,000	447
FY 1991	74,559,000	438
FY 1992	79,653,000	457
FY 1993	82,449,000	460
FY 1994	81,841,000	480

Rationale for Budget Request

The FY 1995 request for the intramural research program is $83,431,000 and 462 FTEs, an increase of 1.9 percent over the FY 1994 estimate of $81,841,000 and a decrease of 18 in the number of FTEs. The increase in Intramural Research reflects a high priority that the NIDDK places on women's health in general and breast cancer in particular. The NIDDK has pursued a careful but aggressive growth in research on the endocrine aspects of breast cancer within the 1994 appropriation and is requesting a program increase in this area in FY 1995. This will allow the NIDDK to expand existing efforts and pursue new opportunities in FY 1995. The fundamental research and clinical studies supported by the intramural research program help to provide a solid base of knowledge for the development of improved methods to treat and prevent disease. The flexibility of the program allows investigators to pursue long-term objectives and to follow new research leads rapidly. Hospital facilities located near laboratories for basic research and the proximity of experts in various areas of research foster a rich exchange between lab and clinic and among scientific disciplines. Thus, research advances at the molecular and cellular level can lead quickly to new avenues for the prevention and treatment of a vast array of human diseases. The following are examples of advances in ongoing investigations within the NIDDK Division of Intramural Research:

Diabetes Treatment: Preliminary clinical studies have indicated that administration of insulin-like growth factor I (IGF-I) lowers the requirement for insulin in patients with diabetes mellitus. Although IGF-I will probably not be a replacement for insulin in diabetes treatment, and may prove to have undesirable side effects, it may be a useful addition to insulin in cases that are not otherwise controllable.

Genetics of Diabetes: A genetic mutation associated with insulin resistance and greater prevalence of parental diabetes was identified in the Pima Indians. Insulin resistance and parental diabetes both imply an increased risk of non-insulin-dependent diabetes mellitus.

Complications of Diabetes: Researchers isolated key molecular components in the breakdown of fat, a reaction that becomes disordered in diabetic individuals; and the presence of advanced glycosylation end products--biochemical products that form when blood sugar levels are high--were shown to stimulate scarring in the kidneys of mice.

Thyroid Disease and Behavior/Learning Disorders: A high prevalence of attention deficit hyperactivity disorder, language problems, and lower intelligence quotient was discovered among patients with generalized resistance to thyroid hormone (GRTH). Investigators are also collaborating in newborn screening studies with the goal of developing methods to diagnose GRTH from blood spots.

Familial Male Precocious Puberty: Researchers identified a single change in the DNA that encodes the receptor for luteinizing hormone in the testes of children with familial male precocious puberty. The genetic flaw causes one amino acid to be replaced by another, subtly altering the internal structure of the receptor and triggering the early, inappropriate manufacture of testosterone, without the hormonal signal from the brain. Thus, familial male precocious puberty is an example of an inherited human disease caused by a mutation that activates, rather than blocks, a hormone receptor.

Tay Sachs Disease: Promising results were achieved toward development of a "Tay-Sachs mouse." NIDDK investigators have begun to breed mice in which the gene for beta-hexosaminidase (the missing enzyme in people with Tay-Sachs disease) has been disabled, causing an inability to produce the enzyme and leading to the brain pathology that is typical of Tay-Sachs and similar diseases in humans. With a Tay-Sachs mouse, scientists could begin to look for methods of introducing the missing enzyme into the central nervous system, perhaps before the genetic defect has caused irreversible damage.

Obesity: From studies using direct measurement of sympathetic nervous system activity by microneurography in Caucasians and Pima Indians, investigators hypothesize that the low sympathetic nervous activity in the Pima Indians and the lack of impact of that activity on metabolic rate may contribute to the pervasive problem of obesity in this population.

Optimum Doses of Vitamins: A laboratory method was developed to address the question of optimal dose of vitamin C, and that method was used to measure how specific human cellular and physiologic functions are regulated by different amounts of that vitamin. With further work, similar methods should be applicable to other vitamins.

Sickle Cell Disease and Beta-Thalassemia: Researchers are studying candidate hemoglobin-altering drugs using a new method to culture, from human peripheral blood, hemoglobin-producing cells that later become mature red blood cells. While patient testing requires several years for each drug or drug combination, the in vitro screening method yields results in a matter of weeks. Further, opportunities for automation of the screening procedures may make it possible to evaluate thousands of compounds each year, eliminate those that are unlikely to work, and move the others rapidly into animal and human studies.

Gene "Insulators": Gene "insulators" were discovered at the junction between active DNA and the adjacent, inactive, and more densely packaged part of the DNA double strand. The researchers conclude that the insulating element, while having no significant stimulatory or inhibitory effects of its own, may be extremely important in preventing genes from being turned on or off accidentally and inappropriately by the activity of surrounding genes in the living cell. This discovery could lead to improved human gene therapy techniques, whereby the genetic material to be inserted into a patient's DNA could be protected from the possibility of inappropriate regulation.

Depression: Recent research has led to a unifying theory of antidepressant action. In animal studies, the investigators found that, after chronic administration (when the antidepressant effect becomes apparent), the various commercially available antidepressant compounds all alter activity of a subtype of glutamate receptor called the N-methyl-D-aspartate (NMDA) receptor. If borne out, this revolutionary finding will change medicine's approach to antidepressant therapy and will provide improved means of testing and developing new drugs.

Imaging of Brain Activity: A newly developed compound, called ioxy, allows imaging of the living brain via single photon emission computed tomography (SPECT) scanning. Because this method of live-brain imaging does not have the limitations of previous methods, the development of ioxy opens up the possibility that small hospitals will be able to use receptor imaging in conscious humans as a tool for the diagnosis of psychiatric disorders and for monitoring the effects of treatment.

Breast Cancer: Studies have begun to explain the complex interactions between IGFs, their binding proteins, and inhibitors of cancer cell proliferation at the molecular level. The studies will lead to a better understanding of the rapid proliferation and poor prognosis of certain tumors and of breast cancer growth inhibition.

Thyroid Cancer: NIDDK researchers are participating in the Phase III clinical trials of recombinant human thyroid-stimulating hormone (rhTSH) for the diagnosis of residual cancer cells in patients being treated for thyroid cancer. These exciting trials result directly from years of molecular research at the NIDDK, during which researchers cloned the gene for thyroid-stimulating hormone, developed methods to produce it in animals, and ascertained its clinical application.

National Institute of Diabetes and Digestive and Kidney Diseases

Research Management and Support

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
178	$24,052,000	180	$24,405,000	180	$25,230,000	---	+$825,000

Support is provided through this activity for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, property control, and travel audit and control, which are most efficiently performed as centralized functions. Other functions included under this activity are the review, management, and negotiation of research and development contracts of the categorical program areas, and support of the three national advisory boards in diabetes, digestive diseases, and kidney and urological diseases.

Funding for the Research Management and Support program during the last five years has been as follows:

	Amount	FTE
FY 1990	22,666,000	168
FY 1991	21,295,000	165
FY 1992	24,470,000	172
FY 1993	24,052,000	178
FY 1994	24,405,000	180

Rationale for the Budget Request

The FY 1995 request for Research Management and Support is $25,230,000 and an employment level of 180 FTEs. This is an increase of $825,000 above the FY 1994 level of $24,405,000.

A major portion of the resources of this activity is devoted to review and approval of grants functions, including professional and support personnel who are responsible for the administration of the Institute's grants activities. The staff assists in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; review and evaluates research and training grant applications for presentation to the NIDDK Advisory Council and provides required Council staff assistance; serves as liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations; and provides continuous surveillance of scientific information relevant to all transactions.

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	73	71	73
Division of Diabetes, Endocrinology and Metabolic Diseases	19	21	20
Division of Digestive Diseases and Nutrition	18	16	16
Division of Kidney, Urologic and Hematologic Diseases	15	16	16
Division of Extramural Activities	53	56	55
Division of Intramural Research	460	480	462
Total	638	660	642

Average GS/GM Grade

1990	10.4
1991	10.5
1992	10.5
1993	10.5
1994	10.5
1995	10.5

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

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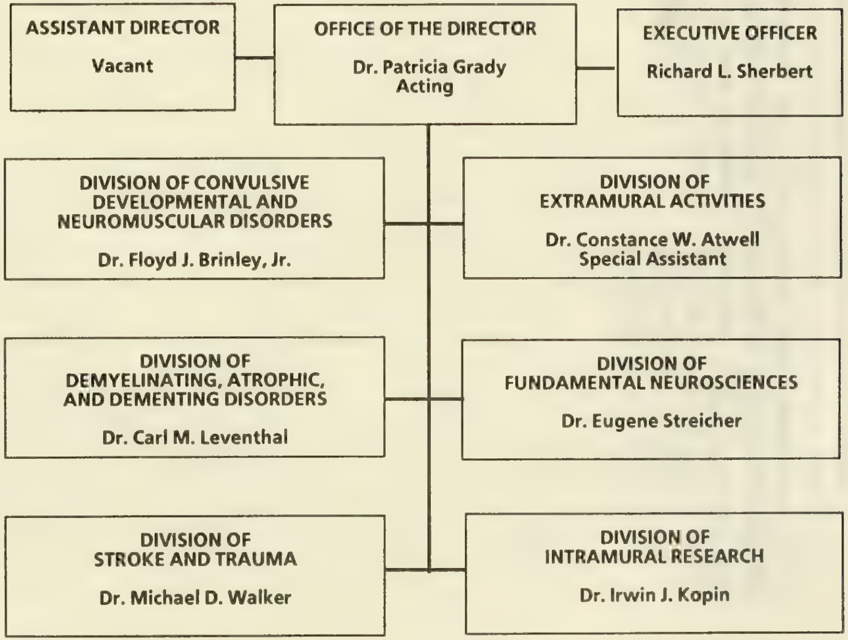
NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Organization Structure


ASSISTANT DIRECTOR
Vacant
OFFICE OF THE DIRECTOR
Dr. Patricia Grady
Acting
EXECUTIVE OFFICER
Richard L. Sherbert
DIVISION OF CONVULSIVE DEVELOPMENTAL AND NEUROMUSCULAR DISORDERS
Dr. Floyd J. Brinley, Jr.
DIVISION OF EXTRAMURAL ACTIVITIES
Dr. Constance W. Atwell
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DIVISION OF DEMYELINATING, ATROPHIC, AND DEMENTING DISORDERS
Dr. Carl M. Leventhal
DIVISION OF FUNDAMENTAL NEUROSCIENCES
Dr. Eugene Streicher
DIVISION OF STROKE AND TRAUMA
Dr. Michael D. Walker
DIVISION OF INTRAMURAL RESEARCH
Dr. Irwin J. Kopin

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological disorders and stroke, [$630,650,000] $630,443,000 *of which $6,844,000 shall not become available for obligation until September 19, 1995.* (Department of Health and Human Services Appropriation Act, 1994.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Language Analysis

Language Provision	Explanation
".... of which 6,844,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$606,600,000	$630,650,000	$630,443,000
Section 511 .8% reduction	-4,853,000	---	---
Section 513 Consultant Services Reduction	-7,000	---	---
Section 216 S&E reduction	-1,662,000	---	---
Subtotal, adjusted appropriation	600,078,000	630,650,000	630,443,000
Real transfer:			
Tuberculosis Research	-590,000	---	---
Comparable transfer to the NIH Office of AIDS Research for HIV Activities	-18,416,000	-22,105,000	---
Subtotal, adjusted budget authority	581,072,000	608,545,000	630,443,000
Unobligated balance lapsing	-22,000	---	---
Total obligations	581,050,000	608,545,000	630,443,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1993 -- $1,859,000; FY 1994 -- $4,400,000 and FY 1995 -- $4,400,000. Excludes $66,758 for Royalties in FY 1993 and $53,000 in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting projects	1325	$306,346,000	1367	$327,455,000	1142	$310,013,000
Administrative supplementals	(54)	1,286,000	(40)	1,628,000	(40)	1,695,000
Competing projects:						
Competing renewals	206	53,000,000	188	53,521,000	242	71,548,000
New	222	41,530,000	203	42,040,000	261	56,199,000
Supplemental	6	454,000	6	597,000	7	798,000
Subtotal, competing	434	94,984,000	397	96,158,000	510	128,545,000
Subtotal, research projects	1759	402,616,000	1764	425,241,000	1652	440,253,000
Research Centers:						
Specialized/comprehensive ctrs	44	31,203,000	46	34,510,000	46	38,227,000
Other Research:						
Research career programs	187	14,699,000	206	16,829,000	206	17,301,000
Cooperative clinical research	1	1,074,000	3	2,303,000	4	3,355,000
Minority Biomedical Support		290,000		221,000		235,000
Other research related	30	2,192,000	43	1,640,000	43	1,686,000
Subtotal, other research	218	18,255,000	252	20,993,000	253	22,577,000
Total, research grants	2021	452,074,000	2062	480,744,000	1951	501,057,000

Training						
Individual awards						
Noncompeting..................	74	2,040,000	72	1,944,000	75	2,115,000
Competing.....................	87	2,225,000	96	2,729,000	93	2,722,000
Subtotal, individual........	161	4,265,000	168	4,673,000	168	4,837,000
Institutional awards						
Noncompeting..................	308	7,616,000	283	7,066,000	265	6,845,000
Competing.....................	34	1,429,000	70	1,979,000	88	2,517,000
Subtotal, institutional.....	342	9,045,000	353	9,045,000	353	9,362,000
Total, training.................	503	13,310,000	521	13,718,000	521	14,199,000
Research & Development Contracts..	50	16,571,000	49	16,812,000	49	17,282,000
	FTEs		FTEs		FTEs	
Intramural Research..............	503	72,563,000	521	71,455,000	503	71,411,000
Research Management and Support...	206	26,554,000	195	25,816,000	193	26,494,000
Total........................	709	581,072,000	716	608,545,000	696	630,443,000
Clinical Trials..............		(37,744,000)		(41,944,000)		(46,620,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Summary of Changes

1994 Estimated budget authority	$608,545,000
1995 Estimated budget authority	630,443,000
Net change	+21,898,000

	1994 Current Estimate Base		Change from Base	
Changes:	(FTEs)	Budget Authority	(FTEs)	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$30,101,000		+$370,000
b. Annualization of Jan. 1994 Locality Pay		30,101,000		+257,000
c. January 1995 pay increases		30,101,000		+396,000
d. Payment for centrally furnished services		26,969,000		+1,195,000
e. Service and supply fund increase		2,759,000		+95,000
f. One less day of pay		30,101,000		-117,000
g. FTS		94,000		+7,000
h. Laboratory supplies, materials and other expenses		14,385,000		+327,000
2. Research Management & Support				
a. Within grade increase		11,491,000		+163,000
b. Annualization of Jan. 1994 Locality Pay		11,491,000		+72,000
c. January 1995 pay increases		11,491,000		+151,000
d. Payment for centrally furnished services		5,224,000		+535,000
e. Service and supply fund increase		2,028,000		+63,000
f. One less day of pay		11,491,000		-45,000
g. DHHS Working Capital Fund		609,000		+5,000
h. FTS		40,000		+3,000
i. Unemployment Compensation and FECF		159,000		+22,000
j. Supplies, materials and other expenses		9,078,000		+198,000
Subtotal		--		+3,697,000

	1994 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting.............	1,367	329,083,000	-225	-17,375,000
b. Competing................	397	96,158,000	+113	+32,387,000
Total....................	1,764	425,241,000	-112	+15,012,000
2. Research centers..............	46	34,510,000	--	+3,717,000
3. Other research................	252	20,993,000	+1	+1,584,000
4. Research training.............	521	13,718,000	--	+481,000
5. Research and development contracts..................	49	16,812,000	--	+470,000
Subtotal, extramural.........	2,632	511,274,000	-111	+21,264,000
	(FTEs)		(FTEs)	
6. Intramural research...........	(521)	71,455,000	(-18)	-2,574,000
7. Research management and support.....................	(195)	25,816,000	(-2)	-489,000
Subtotal..................		--		+18,201,000
Total changes.........		--		+21,898,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	716	696	-20
Full-time equivalent of overtime and holiday hours	4	4	---
Average ES salary	$109,129	$110,875	+$1,746
Average GM/GS grade	9.9	9.9	---
Average GM/GS salary	45,231	46,782	+1,551
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207) ..	72,957	74,124	+1,167
Average salary of ungraded positions .	24,033	24,857	+824
Personnel compensation:			
Full-time permanent	$21,155,000	$21,188,000	+$33,000
Other than full-time permanent	8,426,000	8,404,000	-22,000
Other personnel compensation	1,382,000	1,400,000	+18,000
Special personal services payments .	3,307,000	3,340,000	+33,000
Subtotal, personnel compensation .	34,270,000	34,332,000	+62,000
Personnel benefits	7,214,000	6,942,000	-272,000
Benefits for former employees	26,000	27,000	+1,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Travel and transportation of persons .	$1,060,000	$1,060,000	---
Transportation of things	154,000	138,000	-16,000
Rent, communications and utilities:			
Rental payments to other than GSA ..	8,000	8,000	---
Communications, utilities, and miscellaneous charges	1,375,000	1,371,000	-4,000
Subtotal, rent,communications ..... & utilities	1,383,000	1,379,000	-4,000
Printing and reproduction	342,000	322,000	-20,000
Other services:			
Consulting service	111,000	113,000	+2,000
Other services	12,468,000	12,052,000	-416,000
Purchases from Govt. accounts	32,643,000	33,966,000	+1,323,000
Operation of GOCOs	800,000	800,000	---
R & D contracts	16,362,000	16,832,000	+470,000
Supplies and materials	4,212,000	4,105,000	-107,000
Equipment	3,037,000	3,119,000	+82,000
Grants, subsidies, and contributions .	494,462,000	515,256,000	+20,794,000
Interest	1,000	0	-1,000
Total	608,545,000	630,443,000	+21,898,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NINDS

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	21,155	21,155	21,188	33
11.3	Other than full-time permanent	8,426	8,426	8,404	(22)
11.5	Other personnel compensation	1,382	1,382	1,400	18
11.8	Special personnel services payments	3,307	3,307	3,340	33
11.9	Subtotal, personnel compensation	34,270	34,270	34,332	62
12.1	Civilian personnel benefits	7,214	7,214	6,942	(272)
13.0	Benefits for former personnel	26	26	27	1
	Subtotal Pay Costs	41,510	41,510	41,301	(209)
21.0	Travel and transportation of persons	1,189	1,060	1,060	0
22.0	Transportation of things	118	154	138	(16)
23.2	Rental payments to others	4	8	8	0
23.3	Communications, utilities, and miscellaneous charges	1,385	1,375	1,371	(4)
24.0	Printing and reproduction	232	342	322	(20)
25.0	Other Services	45,933	42,666	43,575	909
26.0	Supplies and materials	4,212	4,212	4,105	(107)
	Subtotal non-pay costs	53,073	49,817	50,579	762
	Total Administrative Costs	94,583	91,327	91,880	553

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action taken or to be Taken
1994 House Report	
Epilepsy	
1. The House in its report 103-156, page 58 stated, "The Committee encourages the Institute to apply new methods of basic research to the study of epilepsy."	1. The Institute issued a program announcement in March 1993 soliciting research grants utilizing new methods to study the genetic factors involved in epilepsy. The responses to this program announcement will enable NINDS to support research utilizing these new methods of studying epilepsy. The Institute also plans to revise and reissue an existing program announcement on basic mechanisms of epilepsy. Intramural investigations include study of nerve cell receptors that may be involved in epilepsy and methods to control their activity.
Stroke	
2. The House in its report 103-156, page 58 stated, "The Committee has heard testimony concerning the growing incidence of stroke among post-menstrual women and minorities and in the area of the country called the "stroke belt." This is particularly distressing because stroke is currently among the leading causes of death in our country. The Committee is supportive of research in this area."	2. Stroke remains the third leading cause of death in the United States. The stroke age-adjusted death rate for men and women is approximately the same; only in women 85 years of age and older does the age-adjusted stroke death rate exceed that of men in the same age group. However, the total number of strokes causing death is greater in women due to their living on an average 6.9 years longer than men. The "stroke belt", which has a stroke rate at least 10 percent higher than the national age-adjusted stroke rate, includes South Carolina, Georgia, Mississippi, North Carolina, Arkansas, Louisiana, Alabama, Tennessee, Kentucky, Indiana and Virginia as well as the District of Columbia. The age-adjusted stroke death rate for black women (40.3 per 100,000) is less than for black men (52.1 per 100,000), but black men and women have a considerably higher stroke death rate

Item	Action taken or to be Taken
	than the United States at large (26.1 per 100,000). The NINDS is currently funding three epidemiologic studies aimed at determining the differences in stroke rate among different populations within the U.S. and further evaluating the interrelationship of stroke risk factors. In addition, preliminary data are being analyzed from a study nearing completion in the "stroke belt" in order to determine whether there are different types of strokes experienced by minority populations. These studies will help to direct future research in this complex arena. There is a growing body of evidence that suggests that postmenopausal women may have an increased stroke rate. In order to investigate the interrelationship of estrogen and stroke, a clinical trial has been initiated to study the use of estrogen to decrease the risk of stroke in post menopausal women who have already had a stroke.
Neurofibromatosis	
3. The House in its report 103-156, page 58 stated, "The Committee recognizes that recent advances in NF research, including the discovery of the NF genes and their connection to cancer, open up exciting new opportunities to find a treatment and cure not only for NF, but also for cancer, brain tumors and other disorders now affecting over 100 million Americans. These research opportunities include the development of an NF animal model, further determination of the role of the NF genes in producing the many severe problems seen in NF and further	3. A program announcement released jointly with NCI in FY 92 has led to the funding of new research grants. The Institute has prepared a follow-up program announcement soliciting research on neurogenetic disorders including neurofibromatosis.

Item	Action Taken or to be Taken
refinement of the connection between NF and cancer. Accordingly, the Committee supports continued expansion of research on this critical problem. The Committee further recognizes that research into NF is cost-effective because of its interdisciplinary nature."	
Lou Gehrig's disease	
4. The House in its report 103-156, page 58 stated, "Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a neurological condition whose cause, treatment and cure remain unknown. Recently, the gene believed to cause one form of familial ALS was discovered. The Committee urges NINDS to give high priority to ALS research, especially in light of the promising research opportunities."	4. NINDS research efforts in amyotrophic lateral sclerosis (ALS) include studies of genetic factors in ALS, growth factors and their potential therapeutic value, and animal models of the disease. In the past year, NINDS-supported scientists identified a gene responsible for many cases of familial ALS; this finding generated new insights into the mechanisms of ALS as well as other neurodegenerative diseases. In separate studies, defects in the transport of a neurotransmitter, glutamate, have been implicated in the disease; an effort is under way to clone several related transporter genes. Ongoing intramural investigations relevant to ALS include study of the basic neurobiology of calcium-mediated synaptic transmission; results from this research may provide insights to understand physiological defects in ALS tissue. NINDS also actively encourages new and more varied research in ALS and published a program announcement on ALS in February 1993.
Gaucher's disease	
5. The House in its report 103-156, page 58 stated, "The Committee remains committed to a continuation of research on Gaucher's disease, including efforts to develop more affordable treatments."	5. In studies of enzyme replacement therapy, NINDS intramural scientists are investigating whether a maintenance dose that is one-fourth the early, higher dose can keep patients healthy, and to determine the minimum doses needed to improve health in previously untreated Gaucher's

Item	Action Taken or to be Taken
	patients. NINDS scientists are also testing agents that may be used in combination with the enzyme to boost its effectiveness. These efforts are expected to contribute to more affordable treatments. Intramural investigations also include research to develop techniques for transfer and expression of the glucocerebrosidase gene. The first gene therapy trials for Gaucher's disease will be initiated in 1994.
Batten disease	
6. The House in its report 103-156, page 58 stated, "The Committee has heard compelling testimony about Batten disease, a degenerative neurological condition affecting children. The Committee has provided additional funding to increase research support in this area above the 1993 levels."	6. The NINDS expects to increase support for Batten disease research in FY 1994. The NINDS has issued an RFA jointly with NIDDK soliciting individual research grants to explore new methods of gene therapy for genetic metabolic diseases, including Batten disease. In addition, intramural research efforts include studies of the pathogenesis and molecular abnormalities in Batten disease.
Dystonia	
7. The House in its report 103-156, page 59 stated, "The Committee is encouraged by the Institute's ongoing dystonia research effort, including the recent workshop on dystonia. The Committee believes that the Institute can play a leading role in encouraging and focusing dystonia research and urges NINDS to continue to expand its extramural research program in dystonia."	7. NINDS has taken several steps to encourage research in dystonia. In 1991, NINDS issued a program announcement to encourage research on movement disorders, with emphasis on dystonia. A summary from the workshop held in 1993 is expected to prompt new research studies. In addition, the Institute recently prepared a program announcement soliciting research on neurogenetic disorders including movement disorders such as dystonia.
Supranuclear palsy	
8. The House in its report 103-156, page 59 stated, "The Committee has a continuing interest in progressive supranuclear palsy and other movement	8. Characteristic symptoms of progressive supranuclear palsy (PSP) are similar to Parkinson's disease (PD), but also different enough to

Item	Action Taken or to be Taken
disorders. The Committee expects the Institute to be prepared at next year's hearings to discuss its work in this area, including its recommendations on the best mechanisms for moving forward research into this important problem."	distinguish PSP from PD. NINDS efforts in PSP have included a study of the prevalence and natural history of PSP and a program announcement on movement disorders which specifically included PSP. In November, 1993, the NINDS sponsored a workshop to assess the reliability of neuropathological diagnosis in PSP. A case controlled clinical study, which complements the workshop, is examining the accuracy of diagnosis of PSP in clinical centers. The results of the study will be published in 1994. Intramural efforts include studies to characterize the cognitive and motor aspects of patients with PSP. NINDS research emphasizes efforts to understand the neurochemical impairment in PSP and how it might differ from that seen in PD. Such efforts will provide necessary information and insights needed to identify methods of treatment.

Item	Action Taken or to be Taken
1994 Senate Report	
Multiple Sclerosis	
1. The Senate in its report 103-143, page 88 stated, "The Committee urges the NINDS to maintain a vigorous research agenda to understand and treat multiple sclerosis (MS)."	1. NINDS supports and conducts research on many aspects of multiple sclerosis (MS) including studies of clinical disease, pathogenesis, treatment, and basic laboratory studies of animal models. To encourage further studies, a program announcement calling for innovative new research grants was issued in the past year. Intramural investigators have conducted extensive longitudinal studies of the natural history of relapsing-remitting multiple sclerosis (MS) using monthly magnetic resonance imaging (MRI) evaluations. The results of those studies demonstrate that MRI is an effective means of monitoring experimental treatments allowing more rapid assessment of therapies with potential benefit. Last year's announcement of the first treatment for MS encourages further studies to expand treatment opportunities.
Duchenne muscular dystrophy	
2. The Senate in its report 103-143, page 89 stated, "The Committee encourages additional extramural DMD treatment research."	2. In FY 1994, the Institute plans to issue a program announcement soliciting research applications on the genetic and non-genetic therapy of Duchenne muscular dystrophy. NINDS anticipates that the response to the announcement will enable it to support additional research in this area.
Stroke	
3. The Senate in its report 103-143, page 89 stated, "The Committee believes that additional increased funding for stroke research should be provided to enable the NINDS to expand its stroke education program and to continue and initiate promising research in stroke diagnosis,	3. Increasingly, large multi-centered clinical trials are being organized that are expected to answer long-standing questions of critical importance to stroke patients. In addition, the underpinning of all clinical research is a well-supported basic laboratory research program in

Item	Action Taken or to be Taken
treatment, rehabilitation, and prevention identified by the National Advisory Neurological Disorders and Stroke Council in the "Progress and Promise 1992: Status Report of the Decade of the Brain."	which investigators are intensifying their efforts to understand the molecular mechanisms of stroke, and develop the pharmacologic intervention of the future. With the positive findings of recent clinical trials, there is a renewed vigor and increased interest in understanding the mechanisms of stroke. NINDS will continue efforts to encourage new research studies in stroke. In addition, NINDS plans to publish in 1994 two new brochures on stroke.
Niemann-Pick disease	
4. The Senate in its report 103-143, page 89 stated, "The Committee recognizes the value of continuing basic and clinical research and funding in this disease and encourages further studies, not only as a means of alleviating the burdens imposed on patients and their families, but also to expand the understanding of similar cholesterol metabolism disorders such as atherosclerosis."	4. Niemann-Pick Type C is marked by the accumulation of cholesterol in nerve cells. In the past year, NINDS intramural scientists linked Niemann-Pick Type C disease to a small region of human chromosome 18. This discovery has resulted in greatly improved diagnostic and carrier detection tests. Scientists are continuing the search to pinpoint the precise location of the gene and determine the function of the gene product. These findings may lead to improved treatment for this inherited disorder and yield new insights into the metabolism of cholesterol. In addition, an RFA issued jointly with NIDDK to solicit individual research grants to explore new methods of gene therapy for genetic metabolic diseases includes Niemann-Pick disease.
Neurofibromatosis	
5. The Senate in its report 103-143, page 89-90 stated, "The Committee recognizes that these discoveries in NF research occurring at breathtaking speed, open up new and exciting opportunities to advance research into and find a treatment and cure for NF, cancer, brain tumors, and numerous other neurobiological disorders now affecting over 100 million Americans. Accordingly, the Committee has provided additional funds to expand and advance research into NF."	5. A program announcement released jointly with NCI in FY92 has led to the funding of new research grants. The Institute has prepared a follow-up program announcement soliciting research on neurogenetic disorders including neurofibromatosis.

Item	Action Taken or to be Taken
Parkinson's disease	
6. The Senate in its report 103-143, page 90 stated, "The Committee, therefore, directs that prior to next year's hearings, the NIH submit a report outlining: potential treatment options and progress toward identifying a cause; current funding levels by Institute for supporting Parkinson's-related research; and a plan for developing a coordinated research agenda among the appropriate Institutes. In addition, the Committee urges NINDS to increase funding for research on Parkinson's disease."	6. The NINDS has been assigned lead responsibility for this report which will be submitted prior to the hearings. NINDS supports an intense research effort on the cause and treatment of Parkinson's disease (PD), a major neurological disorder. Research into the causes of PD includes studies of environmental and endogenous toxins, genetic predisposition, and altered motor circuitry and neurochemistry. New epidemiological studies have recently been initiated to discover other possible risk factors in this disorder. Animal models are being used to study the pathophysiology of the disease and develop novel therapies. The search for better therapeutic interventions is also part of this aggressive effort. A major clinical trial began in fiscal year 1994 to study the efficacy of transplanting fetal tissue into patients with advanced PD. Research on other surgical approaches, causing specific focally placed lesions in the motor circuitry of the brain, will also be supported.
Alzheimer's disease	
7. The Senate in its report 103-143, page 90 stated, "The Committee is aware of the very important and fundamental research the Institute supports on Alzheimer's, and expects that the proportion of additional funds allocated for Alzheimer's research by NINDS be consistent with prior year allocations. The Committee is also pleased with the spirit of cooperation developed between NINDS and the National Institute on Aging, and expects that NINDS will lend its judgment and expertise as NIA develops a long-range plan for slowing the progression of Alzheimer's disease.	7. Exciting discoveries in Alzheimer's disease (AD) research have occurred across a broad range of endeavors. Promising areas of rapid development include the molecular genetics of AD, the role of neurotrophic factors, and the biochemical and immunochemical analysis of the neuropathological characteristics which define AD. The NINDS will continue this momentum by supporting and conducting research in exciting areas such as these, and by continued cooperation with National Institute of Aging (NIA) and other agencies. Staff from NINDS and NIA

Item	Action Taken or to be Taken
	interact regularly to ensure that grant proposals of highest quality are supported and duplication of efforts is minimized. NINDS will continue to lend expertise and judgment as the NIA develops a long range plan for slowing the progress of Alzheimer's disease.
Lou Gehrig's disease	
8. The Senate in its report 103-143, page 90 stated, "The Committee urges the Institute to give high priority to ALS research, especially in light of the promising research opportunities."	8. NINDS research efforts in amyotrophic lateral sclerosis (ALS) include studies of genetic factors in ALS, growth factors and their potential therapeutic value, and animal models of the disease. In the past year, NINDS-supported scientists identified a gene responsible for many cases of familial ALS; this finding generated new insights into the mechanisms of ALS as well as other neurodegenerative diseases. In separate studies, defects in the transport of a neurotransmitter, glutamate, have been implicated in the disease; an effort is under way to clone several related transporter genes. Ongoing intramural investigations relevant to ALS include study of the basic neurobiology of calcium-mediated synaptic transmission; results from this research may provide insights to understand physiological defects in ALS tissue. NINDS also actively encourages new and more varied research in ALS and published a program announcement on ALS in February 1993.
Pediatric positron emission tomography (PET) research	
9. The Senate in its report 103-143, page 90 stated, "The Committee encourages the Institute to expand support for research regarding the diagnostic applications of positron emission tomography in children and to utilize the expertise of PET	9. Brain imaging studies have provided important research information on neurodevelopmental disorders. Positron emission tomography (PET), which involves the use of radioactive tracers, is sufficiently safe to be employed with

Item	Action Taken or to be Taken
facilities dedicated to the treatment of children's diseases and affiliated with other medical research and teaching institutions."	children where there is justification for medical reasons. Intramural investigators are using PET to study Lennox-Gastaut syndrome, a severe form of epilepsy, and to study children with less severe epilepsy to study the development of the brain and how it is affected by the seizures. The NINDS welcomes applications for research support that would expand the use of PET in research on childhood neurological conditions.
Dystonia	
10. The Senate in its report 103-143, page 90 stated, "The Committee is particularly interested in support for research which is directed toward finding the gene and understanding brain function with specific relevance to dystonia."	10. NINDS has taken several steps to encourage research in dystonia. In 1991, NINDS issued a program announcement to encourage research on movement disorders, with emphasis on dystonia. A summary from the workshop held in 1993 is expected to prompt new research studies. In addition, the Institute recently prepared a program announcement soliciting research on neurogenetic disorders including movement disorders such as dystonia.
Brain tumors	
11. The Senate in its report 103-143, page 91 stated, "The Committee recognizes the need to increase support for research to identify the causes and effective treatments of this devastating disease and has included sufficient funds for the Institute to expand support for basic and clinical research in brain tumors and for training neurooncologists."	11. Major ongoing efforts in brain tumor research include separate intramural studies of a novel genetic therapy and immunotoxin therapy for brain tumors. While it is too early to determine the beneficial effects of the genetic therapy, it is a clear example of collaborative efforts to develop gene transfer technology, test it in appropriate animal studies, and carry out clinical pilot studies. The Institute intends to continue to explore this important, new, and different form of treatment. In addition, feasibility centers in brain tumor research, first funded in FY 1992, have demonstrated enthusiasm with impressive advances toward the accomplishment of their goals to become fully-supported clinical research centers.

Item	Action TAken or to be Taken
Batten disease	
12. The Senate in its report 103-143, page 91 stated, "The Committee has included sufficient funds for NINDS to expand its research in this area over the previous year's level, to continue existing grants, and to provide opportunities for new research grants."	12. The NINDS expects to increase support for Batten disease research in FY 1994. The NINDS has issued an RFA jointly with NIDDK soliciting individual research grants to explore new methods of gene therapy for genetic metabolic diseases, including Batten disease. In addition, intramural research efforts include studies of the pathogenesis and molecular abnormalities in Batten disease.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Authorizing Legislation

	PHS Act / Other Citation	U.S Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation..	Section 301	42 241	Indefinite	$594,827,000	Indefinite	$616,244,000
National Institute of Neurological Disorders and Stroke.................	Sections 457-459	42 285j	Indefinite		Indefinite	
National Research Service Awards.....................	Section 487	42 288	$400,000,000	13,718,000	Such sums as necessary	14,199,000
Total Budget Authority......				608,545,000		630,443,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1986	$375,515,000	$418,590,000	$428,517,000	$433,362,000 1/
1986 Sequester	---	---	---	-18,635,000
1987	399,351,000	491,085,000	487,218,000	490,233,000
1988	423,193,000	554,039,000	550,172,000	534,692,000 2/
1989 3/	557,585,000	557,046,000	477,878,000	567,690,000
1990	493,502,000	495,225,000	498,988,000	495,625,000 4/
1990 Sequester	---	---	---	-5,216,000
1991 5/	512,212,000	545,225,000	555,488,000	541,743,000 6/
1991 Sequester	---	---	---	-7,000
1992	583,355,000	583,355,000	583,386,000	577,938,000 7/
1993	615,190,000	605,100,000	607,100,000	600,078,000 8/
1994	590,065,000	630,650,000	630,650,000	630,650,000
1995 9/	630,443,000			

1/ Excludes an administrative reduction of $233,000.

2/ Includes funds for a reduction of $174,000 for travel and transportation costs.

3/ The House allowance excludes $14,210,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSAs. It excluded $93,100,000 for Other Communication Disorders (NIDCD). The appropriation included the budget for the NRSA program and provided $96,100,000 for the establishment of the proposed new institute, NIDCD.

4/ Excludes an enacted administrative reduction of $1,471,000.

5/ The House allowance excluded $13,016,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSAs.

6/ Excludes enacted administrative reductions of $15,121,000.

7/ Excludes enacted administrative reductions of $4,391,000 and an enacted rescission of $1,049,000.

8/ Excludes enacted administrative reductions of $6,522,000.

9/ Excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Biological Basis research........	---	$278,321	---	$284,791	---	$291,731	---	$308,265	---	$320,930	---	+$12,665
Clinical research.	---	155,083	---	181,652	---	190,224	---	203,009	---	211,608	---	+8,599
Total extramural		433,404		466,443		481,955		511,274		532,538		+21,264
Intramural research.	537	67,863	540	70,934	503	72,563	521	71,455	503	71,411	-18	-44
Research management and support.......	203	24,395	209	25,821	206	26,532	195	25,816	193	26,494	-2	+678
Total, obligations..	740	525,662	749	563,198	709	581,050	716	608,545	696	630,443	-20	+21,898
Unobligated balance, lapsing...........		12		8		22		---		---		---
Total budget authority.......	740	525,674	749	563,206	709	581,072	716	608,545	696	630,443	-20	+21,898

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Neurological Disorders and Stroke

1993 Actual		1994 Appropriation		1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
709	$581,072,000	716	$608,545,000	696	$630,443,000	-20	+$21,898,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of Neurological Disorders and Stroke. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The nervous system connects us to the world. A healthy nervous system enables us to hear, see, taste, think, learn, remember, and walk. In partnership with other body systems, the nervous system helps to perform functions such as digestion, sleep, blood circulation, and reproduction. Disruption--due to infections, trauma, missing genes, toxins from the environment, or lack of adequate blood supply--results in a diversity of neurological disorders that affect every age and population group in the United States, and can result in death or neurological disability. For example, stroke is the the third leading cause of death in the U.S. An estimated twenty-five percent of all genetic disorders affect the nervous system. Epilepsy affects approximately one percent of the population. Permanent neurological disability that restricts daily activities affects about 50 million Americans and costs the country $400 billion each year.

Until very recently, the reality--or hope--for a cure or a way to prevent neurological disorders, ameliorate their disabling consequences, or foster recovery was quite limited. Today, however, we can point to tremendous accomplishments and extensive research opportunities for further progress across the spectrum of a range of disorders. Within the past few years the horizon has become brightly illuminated with discoveries of the risk factors for many neurological disorders, identification of genes active in the nervous system, discovery of a "window-of-opportunity" following trauma to the nervous system in which further cell and tissue damage can be prevented, and discovery of normally-occurring enzymes, growth factors, and other substances that encourage healthy growth and function of the nervous system. Scientists have identified destructive mechanisms that may play a role in neurological disorders as diverse as Huntington's disease, trauma, and stroke. These discoveries have been enabled, in part, by revolutionary advances in brain imaging, cell culture and recording techniques, and molecular genetics that allow investigators to probe the structure and function of the nervous system.

The National Institute of Neurological Disorders and Stroke (NINDS) is the lead Federal agency for the support and conduct of research and research training on the normal function of the brain, spinal cord, and peripheral nerves, and neurological and neuromuscular disorders. NINDS scientists and grantees in laboratories, hospitals, and universities across the country seek to understand the human brain and find ways to prevent and treat over 600 neurological disorders including stroke, epilepsy, multiple sclerosis, head and spinal cord injury, Alzheimer's disease and other dementias, neuro-AIDS, muscular dystrophy, Parkinson's disease, neurofibromatosis, and Huntington's disease.

Continued progress in understanding the brain will benefit people with--or at risk for--neurological and neuromuscular disorders through improved diagnoses, new methods for prevention and treatment, strategies to delay the progression of degenerative disorders of the nervous system, and prosthetic devices to interface with the nervous system to restore function. Specific areas of research in 1995 will include:

•Stroke: Medical and surgical methods to prevent stroke in selected populations have been demonstrated. Ongoing clinical trials and laboratory studies promise benefit to even more people with, or at risk for, stroke.

•Neonatal and Child health: Research will include studies to apply the powers of brain imaging techniques and the knowledge gained from study of trauma to the adult brain to the study of neonatal brain injury. Four pilot research centers for the study of neonatal brain injury have been established. Recent findings from an epidemiology study show that twins are at higher risk for cerebral palsy; 12 twin pregnancies per 1,000 are affected compared to 1.1 per thousand single pregnancies.

•Neurodegenerative disorders: Recent discoveries to understand neurodegenerative disorders include the identification of genes for Huntington's disease and familial amyotrophic lateral sclerosis (ALS). The finding that the familial ALS gene produces an enzyme that normally neutralizes the effects of oxygen free radicals has opened exciting new leads which will be pursued in research on ALS and other debilitating neurological disorders.

•Neurogenetics: The need and opportunity to understand the genetic basis of the nervous system permeate every area of neurological research. More genes have been discovered for disorders of the nervous system than any other system. The search for others continues: for example, intramural investigators narrowed the search for the gene for Niemann-Pick disease. For other disorders, such as multiple sclerosis and some forms of epilepsy, genetic factors may play a role in the disease. Research on genetic therapy includes a novel approach undertaken by intramural scientists to treat brain tumors.

•Trauma: Research emphases will include prevention of secondary damage following trauma and methods to repair and restore nervous system function. These approaches offer the chance to improve recovery and facilitate return to the normal activities of daily living.

The President's appropriation request of $630,443,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Neurological Disorders and Stroke during the last five years has been as follows:

	Amount	FTE
FY 1990	$473,182,000	677
FY 1991	525,674,000	740
FY 1992	563,206,000	749
FY 1993	581,072,000	709
FY 1994	608,545,000	716

Purpose and Method of Operation

Biological Basis Research stimulates and supports research on the structure and function of neurological systems. Technology transfer and communication among investigators are fostered by support of research workshops, symposia, and conferences. Support is provided through research grants, Research Career Program Awards, research and development contracts, and National Research Service Awards.

Clinical Research seeks to clarify pathological conditions and develop methods for diagnosis, treatment, and prevention of these conditions. Studies involve not only clinical investigations in humans, but also preclinical research to develop disease models, diagnostic tests, prosthetic devices, and treatments. This activity is supported through research grants, research centers, research and development contracts, Research Career Program awards, and National Research Service Awards.

The Intramural Research program conducts fundamental studies on nerve cell development, structure, and function as well as clinical research studies aimed at improved methods for the prevention, diagnosis, and treatment of neurological disorders. The basic approaches involve molecular genetics, cell biology, neurochemistry, and biophysics. The clinical investigations include studies of virology, immunology, epidemiology, neurology and neurosurgery and brain imaging technology directed toward the prevention or treatment of nervous system disorders.

The Institute's research training budget supports Individual National Research Service Awards (NRSA) and Institutional NRSAs in selected research disciplines of national shortage. These programs train personnel for academic careers in research aimed at developing improved diagnosis, treatment and, where possible, prevention of human nervous system disorders.

Through the Research Career Program, specifically the Research Career Development Award (RCDA), the Institute promotes and supports career development of neurological scientists. Awards provide salary support to enhance the research capability of individuals who have demonstrated outstanding potential for contributing as independent research investigators. The Research Career Program, through Clinical Investigator Development Awards (CIDA), seeks to recruit and prepare future physician investigators for academic research careers in the neurological sciences. The NINDS has established a program for re-entry into the neurological sciences (RENS) to help scientists who have experienced an interruption in their research careers to return to active careers in neurological sciences research. The Neurological Sciences Academic Development Award (NSADA), an institutional award, has been established on a pilot basis in pediatric neurology for physicians in residency training to have exposure to research career opportunities.

Research Management and Support includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions for research grant, research contract, and research training programs. This activity also supports the Office of the Director staff involved in management and direction of the Institute's programs.

Overall Budget Policy

The FY 1995 budget request for the NINDS is $630,443,000, an increase of $21,898,000 over the comparable FY 1994 level.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The NINDS FY 1995 budget request for research project grants is $440,253,000, an increase of $15,012,000 over the FY 1994 comparable level. This represents an increase of 3.5 percent. The total number of research project grants in FY 1995 is 1652, as compared to 1764 in the FY 1994 comparable level. Average costs of competing research project grants would receive an increase equal to the Biomedical Research and Development Price Index (BRDPI) of 4.1 percent.

In FY 1995, the Institute will support 46 centers for $38,227,000, the same number as the comparable FY 1994 level.

Other research grants will total 253 awards for $22,577,000, in FY 1995, an increase of one grant above the comparable FY 1994 level. For National Research Service Awards, an estimated 521 research trainees will be supported in FY 1995, the same number as in the comparable FY 1994.

The research and development contract budget of $17,282,000, will support 49 contracts, the same number as the comparable FY 1994 level.

The FY 1995 budget request for intramural research is $71,411,000, a decrease of $44,000 from the comparable FY 1994 level. The request for research management and support is $26,494,000, an increase of $678,000 over the comparable FY 1994 dollar level.

National Institute of Neurological Disorders and Stroke

Extramural Research

Authorizing Legislation - Sections 301 and 457-459 of the Public Health Service Act. 1994 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$481,955,000	$511,274,000	$532,538,000	+$21,264,000

This program includes research on the fundamental structure and function of the brain and nervous system; the causes and mechanisms of dysfunction of the nervous system; and research training in the basic neurological sciences. Clinical research is directed towards the solution of problems directly relevant to patients, including improved methods of diagnosis and prevention; development of treatments including drugs and surgery; development of neural prosthetic devices; epidemiological research; and research training in the clinical neurological sciences.

Funding for Extramural Research during the last five years has been as follows:

	Amount
FY 1990	$392,092,000
FY 1991	433,392,000
FY 1992	466,443,000
FY 1993	481,955,000
FY 1994	511,274,000

Rationale for Budget Request

The FY 1995 request is $532,538,000 an increase of $21,264,000 above the comparable FY 1994 estimate of $511,274,000. With the FY 1995 extramural request these funds will provide support for the following activities: Biological Basis Research, $320,930,000, an increase of $12,665,000 or 4.1 % over the FY 1994 estimate of $308,265,000; Clinical Research, $211,608,000, an increase of $8,599,000 or 4.2 % over the FY 1994 estimate of $203,009,000. The following are examples of research activities that will be funded in the Extramural Research Program.

The Developing Nervous System

Progress in treating and preventing neurological disorders will derive from new and continuing research efforts to understand the normal development and function of the nervous system. Major efforts are directed at delineating the myriad of events and components necessary to construct the mature nervous system with its many specialized cells and intricate connections. For example, studies show that a family of nerve growth factors, or neurotrophics, are involved in the control of proliferation and differentiation of precursor cells in the developing nervous system. In other work, scientists are moving beyond studies of non-specific growth factors in tissue culture to investigations of specific factors which operate in vivo by developing procedures through which such specific growth factors may be identified and isolated. Once cloned, the genes for these factors can be mutated and reinserted into cells or animals, to determine the effect of genetic alterations on the structure and function of the nervous system.

Nerve cells communicate via electrochemical messages released from the extension or axon of one cell and relayed to the next cell. Research on axonal pathfinding and neuronal circuitry is revealing the importance of pioneer neurons in the development of pathways in the mammalian brain. At the molecular level, studies on cellular cues and cell adhesion molecules are providing insights into the mechanisms of growth cone guidance and neuronal recognition which ensure that proper connections are established. One application of this research will be to expand understanding of what happens prenatally to children born with language, learning, and motor disabilities.

Neurogenetics

In development and all through life, genes are constantly being "turned on" or "turned off" to make neurotransmitters, receptors, enzymes and other factors necessary for nerve cells to grow, make connections, and send and receive signals. Major lines of research investigation include efforts to identify genes active in the nervous system, and the factors that regulate gene expression. The applications of this work include the development of novel approaches for the treatment of nervous system disorders.

Extensive opportunities exist to combine probes developed by the molecular genetic approaches with new structural techniques (e.g., field emission scanning microscopy) to understand assembly and function of receptors, channels, molecular motors (for fast axonal transport), and the neuronal secretory apparatus, and to investigate the function of intracellular messengers such as calcium and G proteins. Much of the research into cell signalling phenomena was made possible by the development of techniques such as the patch clamp technique, which enables measurement of electrochemical signals within single cells.

Within the past several years, scientists have identified genes associated with more inherited disorders of the nervous system than any other body system; this sets the stage for discovering the gene product responsible for disease and offers the prospect for prevention or treatment of disease, for instance, through gene therapy or replacement therapy. NINDS will encourage new studies in neurogenetic disorders including neurofibromatosis, movement disorders such as dystonia, and Duchenne muscular dystrophy. Over the past few years, NINDS has worked to build a quality research program in Batten disease. Most recently, the NINDS has issued a request for applications (RFA) jointly with NIDDK soliciting individual research grants to explore new methods of gene therapy for genetic metabolic diseases, including Batten disease.

Brain, Hormones, and the Body's Defense System

The nervous system does not function in isolation from the rest of the body. One of the most intriguing areas in the study of the brain is the relationship between the brain, the immune system, and the endocrine (hormone) system under both normal and disease conditions. For instance, nerve signals can trigger the release of some hormones and hormone imbalances can affect cognitive functions. The NINDS encourages investigations in related areas including studies to understand better the mechanisms for communication among the nervous, immune, and endocrine systems; characterize mechanisms by which viruses can enter and thrive in the central nervous system; and explore the impact of immune deficiencies on the nervous system.

Stroke

An estimated 500,000 strokes occur each year; many of these strokes occur in people who have suffered a previous attack. About one-third of these patients will die, and a third will remain permanently disabled. Black Americans experience a higher incidence of stroke, suffer more severe strokes, and are 2.5 times as likely to die from a stroke compared to white Americans. Medical and nursing care, physical therapy, lost income, and other expenses due to stroke cost the nation more than $25 billion annually.

The major brain damage from stroke occurs within the first few hours of a stroke. Some of the damage is due to loss of blood as well as secondary changes within the nerve cells. Several causes have already been found including the entry of small but toxic amounts of calcium, sodium, or other particles into the nerve cell, the generation of destructive molecules by nerve cells, and delayed influences on metabolism. These findings provide exciting leads to develop methods to intervene and prevent many of the damaging effects of stroke.

Prevention of stroke encompasses the prevention of an initial stroke and recurrent stroke, as well as strategies to limit any resulting neurological damage. Efforts to prevent stroke are furthered by research findings that increase awareness of the risk factors for stroke, and awareness of the early signs of impending stroke that necessitate prompt medical treatment. Stroke can be prevented, as shown by NINDS-supported clinical trials that demonstrated the benefit of medical and surgical approaches to prevent stroke in selected patient populations. For example, stroke risk could be cut by 50 to 80 percent in individuals with atrial fibrillation by treating them with aspirin or an anticlotting agent called warfarin. Employing this treatment could prevent about 20,000 to 30,000 strokes a year. In the area of prevention, a major national study will determine the value of blood thinners for reducing stroke, while minimizing hemorrhagic complications in stroke-prone patients who have atrial fibrillation. Another prevention study continues to evaluate the use of a surgical procedure for avoiding stroke altogether, and a third continues to examine the use of that same procedure to reduce the rate of second strokes in patients who have a moderate degree of blockage of their carotid artery. The NINDS has initiated a clinical trial to study the use of estrogen to decrease the risk of stroke in post menopausal women who have already had a stroke.

Neonatal Brain Injury

Neonatal brain injuries can stem from genetic, environmental and metabolic factors that adversely affect neurological development and function and contribute to infant mortality and morbidity. Research on neonatal brain injury includes a focus on brain hemorrhage, disorders of the white matter of the neonatal brain, congenital hydrocephalus, and neonatal seizures. As a disproportionate share of minority infants are born early and underweight, they are at risk for many of these conditions and the developmental disabilities that are a consequence. NINDS supported studies include a clinical trial of allopurinol to prevent encephalopathy and seizures in neonates undergoing deep hypothermia during cardiac surgery. Another study will determine the effect of intrauterine cocaine exposure on outcome at birth and whether such exposure is associated with an increased risk of neurobehavioral impairment in children followed until age three.

In FY 1993, the NINDS issued an RFA for exploratory grant applications for the development of research centers on neonatal brain disorders. Four awards were made. The pilot centers employ a spectrum of approaches involving laboratory, animal, brain imaging, molecular biology, and clinical studies to identify and describe the mechanisms of injury to the developing and newborn brain, evaluate their effects, and explore treatment options.

There is evidence that newborns may experience phenomena similar to that which occurs in the adult brain which has been deprived of proper oxygen levels (hypoxia) or blood circulation (ischemia). As with adults, these dynamic processes, though damaging, also present an opportunity to intervene and protect brain cells and preserve brain function. However, research is needed to further define the specific mechanisms of damage in the neonatal brain, determine the impact on neurological function, and explore therapeutic strategies appropriate to the newborn. For example, studies at one of the recently established pilot research centers for neonatal brain injury will measure excitotoxin activity (glutamate) and those findings will be correlated with long term assessments of neurological outcome.

Epilepsy

Twenty million Americans will have at least one seizure during their lives, and 2.5 million will have the disorder of spontaneously recurrent seizures known as epilepsy. Epilepsy research spans studies of basic mechanisms, etiologies, prevention, diagnosis, and treatment. Specific efforts include seizure mechanisms in the developing brain, epidemiology of epilepsy, clinical studies of therapeutic treatments to control epilepsy, surgical therapies of epilepsy, brain imaging studies, and studies of genetic factors in epilepsy. A new antiepileptic medication, Felbamate, was developed with efforts by the extramural and intramural programs.

Findings from epilepsy research demonstrate how basic neurological research contributes to understanding neurological disorders. Epilepsy genes have been localized to chromosomes in three forms of the disorder. For example, the region of chromosome 21 linked to Baltic type progressive myoclonic epilepsy has a gene encoding part of a calcium binding protein. This is an important lead because calcium has been demonstrated to have a role in controlling normal neuronal excitability. The Institute encourages additional studies that use new methods to study the genetic factors involved in epilepsy and new studies on the basic mechanisms of epilepsy.

Bone Marrow Transplantation for Neuronal Storage Disorders

Neuronal storage disorders are due to abnormal or deficient enzyme activity that leads to a build-up of substances in cells throughout the body, leading to progressive dysfunction. NINDS supports a clinical trial of bone marrow transplantation to prevent the progressive mental retardation and neurologic disability of seven neuronal storage diseases: three types of mucopolysaccharidosis (Hunter syndrome, Hurler syndrome, and Sanfilippo syndrome), metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy, and Gaucher type III. The approach is based on evidence that some cells in affected organs originate from bone marrow and are continuously replenished. Transplanted bone marrow provides a source for healthy cells that appear capable of correcting the metabolic disorder.

Brain Tumors

Brain tumor is the second most common malignancy of childhood. There is a second incidence peak at the age of 55, causing the death of over 35,000 patients a year, one-third of whom succumb to primary tumors of the brain.

In an effort to encourage new efforts in brain tumor research, eight developmental grants were awarded in 1992 to establish pilot brain tumor research centers that would have the opportunity to develop the necessary collaborative arrangements, interdisciplinary research, and preliminary data to be able to effectively compete for full scale clinical research centers. The first such applications are anticipated for review and funding consideration in FY 1995. A collaborative effort with the National Cancer Institute permitted partial funding for an additional eleven applicants. The pilot centers are making impressive progress toward becoming fully-supported clinical research centers.

Head and Spinal Cord Injury

Over 2 million head injuries occur each year. Approximately 100,000 victims die and 500,000 require hospitalization. Traumatic brain injury (TBI) is considered the principal cause of permanent brain damage in young adults and results in 5,000 new cases of epilepsy annually. The economic costs alone approach $25 billion per year. Traumatic spinal cord injury claims approximately 10,000 new victims each year.

Investigators continue to provide histological and physiological pictures of human spinal cord injury that will guide and focus future research. Despite often remarkable preservation of spinal cord tissue after injury, function is often severely compromised. Studies show that diffuse disruption of axons, not cell death, occurs in cases of traumatic central cord syndrome, and progressive demyelination may contribute to loss of function. Research continues in a variety of related areas to explore the use of implanted tissues and growth factors to promote recovery.

Neurological imaging techniques are yielding new insights into traumatic brain injury. Magnetic resonance imaging (MRI) has revealed more extensive damage than had been shown previously with computed tomography. In 1993, NINDS sponsored a workshop on the consequences of traumatic head injury in children which involved discussion of the epidemiology and impact of head injury in children, outcome of head injury, and neurosurgical and neuropsychological perspectives.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a degenerative disease of motor function that affects an estimated 13,000 to 20,000 Americans each year causing progressive paralysis and inevitable early death. Recent reports provide converging new insights into the mechanisms of the disease. In the past year, NINDS-supported scientists identified a gene responsible for many cases of familial ALS. The gene encodes for superoxide dismutase, an enzyme necessary for removal of free radicals--highly reactive molecules that may play a role in several neurological disorders. Another familial ALS gene appears to be located on a different undetermined chromosome, and a juvenile ALS gene has been localized to chromosome 2. These findings suggest that the several familial forms of ALS, and perhaps even sporadic instances, may result from more than one genetic defect. Other studies have shown that the clearance of the neurotransmitter, glutamate, from the nerve synapse is defective in ALS resulting in toxic levels of glutamate. An effort is under way to clone genes for several glutamate transporter proteins. Trophic factors such as ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and brain derived neurotrophic factor (BDNF), have been shown to prevent programmed or axotomy-induced motor neuron death in animal models. These and similar agents are being evaluated for their potential therapeutic value in several neurological disorders.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease of the nervous system presumed to be of autoimmune origin. MS appears to be influenced by a combination of genetic, viral, immune, and perhaps other unknown factors. The myelin which surrounds nerve fibers in the brain and spinal cord is destroyed, fails to re-form, and develops into scar tissue resulting in neurological dysfunction. There are an estimated 250,000 to 300,000 MS patients in the U.S., representing an economic burden believed to be in excess of $2.5 billion annually. Last year, patients received the first news of a treatment--Betaseron--that can reduce flare-ups of MS.

NINDS grantees are vigorously pursuing several research avenues in the search for the cause and new treatments for MS. The cause of MS remains unclear, although there is increasing evidence that genetic factors play an important role in disease susceptibility. Recent reports indicate that several genes influence MS susceptibility. One such gene may be linked to the histocompatibility antigens (HLA), and others are suspected. Recent evidence suggests that both alpha and beta chains of the T cell receptor encoding genes may also be associated with MS. Another susceptibility factor may be sex or hormone related since MS, like most autoimmune disorders, occurs in women more often than in men. Studies of immune characteristics of

MS patients and abnormalities found in animal models will continue. The Institute plans to continue to support fruitful avenues of research such as mechanisms of pathogenesis and plaque formation, role of heat shock proteins, remyelination, genetic susceptibility, clinical studies of cytokines, use of peptides in regulation/blocking of immune responses, development of new monoclonal antibodies, and studies of adhesion molecule function in cell traffic across the blood brain barrier.

The development of magnetic resonance imaging (MRI), has revolutionized the study of MS. Ongoing studies address diagnostic accuracy and the usefulness of MRI in long term prognostic value, utility in evaluation, the relation of lesion pathogenesis to neurological abnormalities, and the value of the brain and spinal cord images for treatment monitoring.

Dementia, including Alzheimer's Disease

Dementia, affecting more than 1 of every 30 Americans, progressively weakens a person's ability to learn new information and to remember and use knowledge already learned. Young and old can be affected by dementia resulting from drugs, trauma, stroke, infections or inherited metabolic disorders. In Alzheimer's disease (AD), selected groups of cells in the brain are affected by cellular and molecular events not fully understood. In the past few years, however, exciting discoveries have occurred across a broad range of endeavors with the promise that this rapid progress will continue. Promising areas include: the molecular genetics of AD, the role of neurotrophic factors, the biochemical and immunochemical analysis of the neuropathological characteristics which define AD, the study of exogenous causative agents, the development of animal models, and novel strategies to clarify the neurological mechanisms of the development, regulation, and maintenance of the cognitive functions affected by AD.

Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder of movement. It severely incapacitates large numbers of adult Americans. PD research supports work on causes, such as: environmental and endogenous toxins, genetic predisposition, and altered motor circuitry and neurochemistry. New epidemiological studies have recently been initiated to discover other possible risk factors in this disorder. Animal models are being used to study the pathophysiology of the disease and develop new therapies. The search for better therapeutic interventions is also part of this aggressive effort. A major clinical trial supported by NINDS has shown that a drug called deprenyl slows the progression of the symptoms of Parkinson's disease and delays the need for stronger drug therapy. Work is continuing to determine if deprenyl and anti-oxidants reduce or neutralize toxins and actually prevent brain cell destruction, determine longer term effects of these compounds, and explore the efficacy of other drugs to treat Parkinson's disease. A major clinical trial has begun to study the efficacy of transplanting fetal tissue into patients with advanced PD. Research on other surgical approaches will also be studied.

Syringomyelia

Syringomyelia is a chronic progressive disease of the spinal cord characterized by formation of cavities which fill with fluid. The disease is associated with sensory confusion and loss and, in some cases, extreme pain. The disease is most likely to afflict young men. The specific treatments which may include surgery and shunts to control the fluid vary from patient to patient according to the cause of the lesion. NINDS supports basic research into the central nervous system which may uncover new information about syringomyelia and other diseases.

Restitution of Function

Approximately 250,000 persons are disabled by stroke in the United States each year. Other individuals with spinal cord injury, head injury, cerebral palsy, Parkinson's disease, multiple sclerosis, and other neurological conditions can also be affected by deficits in sensation, visual perception, mobility, language, and thinking.

Several avenues are being pursued by NINDS grantees to restore nervous system function. One such strategy is the development of neural prostheses--devices that interface with the nervous system to restore sensation or movement. Already this program has yielded: a hand-grip prosthesis that enables paralyzed people to pick up objects or to grasp a cup and drink without assistance; tiny electrodes, measuring about one-third the width of a human hair, that can be implanted inside the body and used to stimulate muscle or nerve cells; new understanding of the nervous system and its pathways that will help scientists place future prostheses in the most effective location; and artificial sensors that may help paralyzed patients to better control movement. NINDS anticipates funding additional investigator-initiated applied, basic, and clinical research on restoration of nervous system function.

Research Training and Career Development

The Institute will continue to encourage and support research training on the fundamental structure and function of the brain and nervous system and the causes and pathophysiology of dysfunction in the nervous system. In the basic neurological sciences, areas of emphasis include molecular biology, cognitive science, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neurosensory physiology and biophysics, and neurovirology. The Institute also provides clinical research training through individual National Research Service Awards and institutional National Research Service Awards. These programs train personnel for academic careers in research aimed at developing improved diagnosis, treatment and, where possible, prevention of human nervous disorders. Major clinical areas of research training include: cerebrovascular disorders (including stroke), medical neurology, neuromuscular disorders, neurosurgery, neuroepidemiology and neuropathology.

Career development in the broad spectrum of the areas of research responsibility of the NINDS is supported through the Research Career Program which includes Research Career Development Awards (RCDA), and Clinical Investigator Development Awards (CIDA). In particular, the CIDA has provided a highly effective method for the recruitment and preparation of future clinical investigators in the neurological disorders and stroke. Through the Research Career Program, the Institute will also promote and support the development of promising young scientists in the following areas: neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neuroradiobiology, neurovirology, neural regeneration and plasticity, neurosensory physiology and biophysics.

National Institute of Neurological Disorders and Stroke

Extramural Research

	1994 Appropriation	1995 Estimate	Change
Impact Data			
Neurological disorders of early life	$76,639,000	$79,791,000	+$3,152,000
Neurological disorders of adult life	40,420,000	42,089,000	+1,669,000
Stroke	64,375,000	67,048,000	+2,673,000
Epilepsy	46,007,000	47,910,000	+1,903,000
Demyelinating disorders	33,311,000	34,688,000	+1,377,000
Neuromuscular disorders	26,105,000	27,181,000	+1,076,000
Infectious diseases of the central nervous system	9,802,000	10,403,000	+601,000
Trauma and injury	68,892,000	71,734,000	+2,842,000
Tumors	10,589,000	11,028,000	+439,000
Disorders due to neurotoxicants .	2,787,000	2,901,000	+114,000
Neuroendocrine and autonomic nervous system	20,932,000	21,787,000	+855,000
Learning, language and behavior .	12,647,000	13,168,000	+521,000
Nervous system function	73,421,000	76,425,000	+3,004,000
Metabolism and nutrition	2,360,000	2,457,000	+97,000
Neurosensory disorders	14,062,000	14,639,000	+577,000
Multicategorical research	8,925,000	9,289,000	+364,000
Total	511,274,000	532,538,000	+21,264,000

National Institute of Neurological Disorders and Stroke

Intramural Research

Authorizing Legislation: Sections 301 and 457-459 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
503	$72,563,000	521	$71,455,000	503	$71,411,000	-18	-$44,000

The research efforts of this program range from fundamental studies on nerve cell development, structure, and function to clinical research aimed at improved methods for the diagnosis, treatment, and prevention of neurological disorders and restitution of function. Intramural clinical studies are primarily in chronic, infectious, or degenerative neurological disorders and typically involve study of a small group of patients over a long period of time. The clinical expertise and available facilities are especially beneficial for the study of the many rare neurological disorders. Intramural studies often involve the development of leading edge technologies and treatments which may include extensive collaborations with extramural investigators and provide a research base for further studies. Research using brain imaging techniques examines the metabolic and anatomic changes in brains of patients with disorders of the nervous system.

Funding for Intramural Research during the last five years has been as follows:

	Amount	FTE
FY 1990	$59,710,000	488
FY 1991	67,875,000	537
FY 1992	70,942,000	540
FY 1993	72,563,000	503
FY 1994	71,455,000	521

Rationale for Budget Request

The FY 1995 budget request for intramural research is $71,411,000, a decrease of $44,000 from the comparable FY 1994 level of $71,455,000. The following are examples of research activities to be funded in the Intramural Research Program.

Novel Treatments for Brain Tumors

Two clinical protocols investigating new approaches to the treatment of malignant brain tumors are nearing completion of the initial phase of study. Genetically engineered proteins that are extremely potent and that have great specificity for tumors compared to normal brain are being delivered using a new approach that permits delivery of very large molecules to the brain and to brain tumors. Most patients who have been treated have shown evidence of a significant tumor response. Results of this study also indicate that this new technique is effective in delivering agents to brain tumors and to the brain in concentrations that were not previously achievable. Research will be expanded to include other types of solid tumors in adults and in children.

Recent preliminary results are encouraging from the first clinical test of an innovative method of gene transfer therapy for brain tumors. The early results of this study suggest that this new approach to treatment is safe, that gene transfer to tumor is occurring in vivo, and that there is antitumor activity. It is too early to determine if this technique will become a beneficial therapy for brain tumors; however, the results are encouraging in that they not only demonstrate that further refinement of this approach may benefit patients with malignant brain tumors, but also suggest that it may be possible to adapt genetic therapy for successful therapy of other cancers.

Dystonia

Intramural scientists are investigating the physiology of patients with dystonia. For instance, studies demonstrate a loss of inhibition in a number of brainstem and spinal reflexes. Studies also continue on the utility and mechanism of action of botulinum toxin treatment for focal hand dystonia.

Mechanisms of Learning and Memory

Multidisciplinary investigations using several animal models explore the question of how information is stored during the process of learning and how it is made available for later recall. By comparing findings from several models, general principles of the biological bases for learning and memory may be uncovered which may be important to understand human cognitive functions. For example, one step in memory formation involves persistent changes in potassium channels in the membranes of specific cells.

Since memory loss is characteristic of Alzheimer's Disease (AD) and potassium channels change during the acquisition of memory, intramural scientists are also investigating potassium channel function as a diagnostic index of AD. Cells (fibroblasts) from AD patients have been found to lack a particular potassium channel that is present in age-matched control patients. The same diagnostic differences have been identified in olfactory neurons from patients. Beta-amyloid applied in low concentrations to control cells was found to cause the same potassium channel differences originally observed in AD patients, implicating beta-amyloid in early memory loss.

Epilepsy

Intramural investigators have developed several new approaches to reduce the excessive excitability that occurs in the brain of epileptic patients without adversely affecting the patient's quality of life. One strategy is to target one type of receptor that mediates nerve cell communication and appears to be involved in epilepsy and seizure development. NINDS scientists have demonstrated that drugs which bind to the ion channel associated with these receptors have potential as antiepileptic agents. One such compound is being developed for human use by intramural researchers in collaboration with a biotechnology company under a CRADA agreement.

National Institute of Neurological Disorders and Stroke

Research Management and Support

Authorizing Legislation: Sections 301 and 457-459 of the Public Health Service Act. 1994 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
206	$26,554,000	195	$25,816,000	193	$26,494,000	-2	+$678,,000

Research Management and Support includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of research grant, research contract, and research training programs. This activity also supports the immediate Office of the Director, and the staff that assists the Director in management and direction of the Institute's programs. These units include the administration and financial management activities of the Institute as well as program analysis functions and scientific and health reporting.

Funding for the Research Management and Support during the last five years has been as follows:

	Amount	FTE
FY 1990	$21,380,000	189
FY 1991	24,395,000	203
FY 1992	25,821,000	209
FY 1993	26,554,000	206
FY 1994	25,816,000	195

Rationale for Budget Request

The FY 1995 budget request for research management and support is $26,494,000, an increase of $678,000 over the comparable FY 1994 level of $25,816,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	73	70	69
Division of Fundamental Neuroscience	10	9	8
Division of Stroke and Trauma	9	9	9
Division of Extramural Activities	67	62	62
Division of Convulsive, Developmental, and Neuromuscular Disorders	40	38	38
Division of Demyelinating, Atrophic, and Dementing Disorders	7	7	7
Division of Intramural Research	503	521	503
Total, NINDS	709	716	696

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Average GS/GM Grade

1990	9.6
1991	9.6
1992	9.7
1993	9.9
1994	9.9
1995	9.9

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

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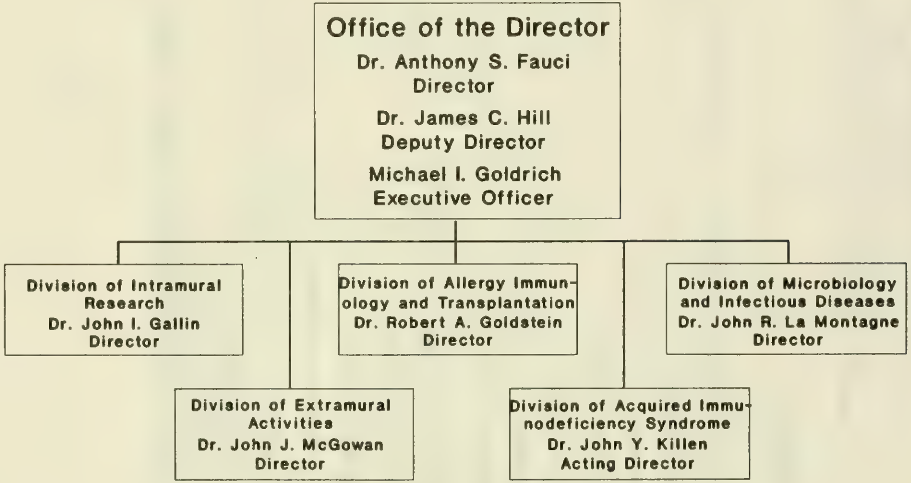
NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Organization Structure



Office of the Director
Dr. Anthony S. Fauci
Director
Dr. James C. Hill
Deputy Director
Michael I. Goldrich
Executive Officer

Division of Intramural Research
Dr. John I. Gallin
Director

Division of Extramural Activities
Dr. John J. McGowan
Director

Division of Allergy Immunology and Transplantation
Dr. Robert A. Goldstein
Director

Division of Acquired Immunodeficiency Syndrome
Dr. John Y. Killen
Acting Director

Division of Microbiology and Infectious Diseases
Dr. John R. La Montagne
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, [$1,065,583,000] *$542,864,000 of which 1,736,000 shall not become available for obligation until September 19, 1995*. *(Department of Health and Human Services Appropriations Act, 1994.)*

National Institute of Allergy and Infectious Diseases

Language Analysis

Language Provision	Explanation
"...of which $11,736,000 shall not become available for obligation until September 19, 1995."	*This language ensures that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$991,805,000	$1,065,583,000	$542,864,000
Section 511 reduction	-7,934,000		
Section 513 consultant services reduction	-37,000		
Section 216 S&E reduction	-4,363,000		
Subtotal, Adjusted appropriation	979,471,000	1,065,583,000	542,864,000
Real transfer from:			
Other Institutes for Tuberculosis research	4,756,000		
Comparative tranfer to:			
NIH Office of AIDS Research for HIV research activities	-459,698,000	-544,791,000	
Subtotal, adjusted budget authority	524,529,000	520,792,000	542,864,000
Unobligated balance, lapsing	113,000	---	---
Total obligations	524,416,000	520,792,000	542,864,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1993 - $11,679,000; 1994 - $15,000,000; 1995 - $29,000,000

Note: Excludes $225,000 for royalties received in 1993 and $275,000 in 1994.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases
Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting.............	1,317	$281,531,000	1,272	$279,105,000	1,149	$262,559,000
Admin. supplemental.......	(23)	972,000	(23)	1,194,000	(23)	1,242,000
Competing						
Renewal................	164	39,037,000	136	32,842,000	206	51,666,000
New....................	211	34,024,000	174	28,495,000	263	44,754,000
Supplemental...........	-	-	-	-	-	-
Subtotal, competing...	375	73,061,000	310	61,337,000	469	96,420,000
Subtotal, research projects..........	1,692	355,564,000	1,582	341,636,000	1,618	360,221,000
Research centers						
Specialized/comprehensive.	3	1,291,000	3	1,279,000	3	1,315,000
Other research						
Research career program...	96	7,121,000	97	7,274,000	97	7,478,000
Minority biomedical support................	--	619,000	--	645,000	--	677,000
Other....................	39	1,591,000	39	1,868,000	39	1,930,000
Subtotal, other research	135	9,331,000	136	9,787,000	136	10,085,000
Total, research grants......	1,830	366,186,000	1,721	352,702,000	1,757	371,621,000

Training						
Individual awards						
Noncompeting	52	1,490,000	75	2,140,000	51	1,443,000
Competing	62	1,726,000	7	149,000	31	910,000
Subtotal, individual	114	3,216,000	82	2,289,000	82	2,353,000
Institutional Awards						
Noncompeting	370	9,640,000	445	12,558,000	396	11,303,000
Competing	189	5,421,000	69	1,619,000	118	3,271,000
Subtotal, institutional	559	15,061,000	514	14,177,000	514	14,574,000
Total, training	673	18,277,000	596	16,466,000	596	16,927,000
R&D Contracts	57	38,236,000	81	53,425,000	83	56,221,000
	FTEs		FTEs		FTEs	
Intramural research	664	75,861,000	651	73,855,000	627	73,888,000
Research management and support	472	25,969,000	493	24,344,000	484	24,207,000
	1,136	524,529,000	1,144	520,792,000	1,111	542,864,000
Clinical Trials		(52,191,000)		(51,148,000)		(52,826,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Summary of Changes

1994 Estimated budget authority	$520,792,000
1995 Estimated budget authority	542,864,000
Net change	+22,072,000

	1994 Current Estimate Base		Change from Base	
Changes:	(FTEs)	Budget Authority	(FTEs)	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$33,737,000		+$434,000
b. One less day of pay		33,737,000		-130,000
c. Annualization of FY 1994 locality pay raise		33,737,000		+230,000
d. January 1995 pay raise		33,737,000		+409,000
e. FECF increase		33,737,000		+15,000
f. Payment for centrally furnished services		16,133,000		+663,000
g. Service and supply fund increase		2,910,000		+149,000
h. FTS increase		70,000		+4,000
i. Increased cost of laboratory materials and supplies		23,985,000		+592,000
Subtotal				+2,366,000
2. Research Management and Support				
a. Within grade increase		$15,625,000		+201,000
b. One less day of pay		15,625,000		-60,000
c. Annualization of FY 1994 locality pay raise		15,625,000		+108,000
d. January 1995 pay raise		15,625,000		+189,000
e. FECF increase		15,625,000		+6,000
f. Payment for centrally furnished services		2,983,000		+123,000
g. Service and supply fund increase		767,000		+38,000
h. Working Capital Fund		518,000		+3,000
i. FTS increase		34,000		+2,000
j. Increased cost of laboratory materials and supplies		5,736,000		+140,000
Subtotal				+750,000

Summary of Changes continued

B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a) Noncompeting	1,272	$280,299,000	-123	-$16,498,000
b) Competing	310	61,337,000	+159	+35,083,000
Subtotal	1,582	341,636,000	+36	+18,585,000
2. Special/Comp Centers	3	1,279,000	---	+36,000
3. Other research	127	9,787,000	---	+298,000
4. Research Training	596	16,466,000	---	+461,000
5. R & D Contracts	81	53,425,000	+2	+2,796,000
Subtotal, extramural	2,389	422,593,000	+38	+22,176,000
	(FTEs)	Amount	(FTEs)	Amount
7. Intramural research	651	73,855,000	-24	-2,333,000
8. Research Management and Support	493	24,344,000	-9	-887,000
Total, changes			-33	+22,072,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Full-time equivalent employment.....	1,144	1,111	-33
Full-time equivalent of overtime and holiday hours................	8	8	---
Average ES salary..................	$104,887	$107,383	+$2,496
Average GM/GS grade.................	10.0	10.0	---
Average GM/GS salary................	44,134	45,184	+1,050
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	73,228	74,971	+1,743
Average salary of ungraded positions	27,484	28,138	+654
Personnel compensation:			
Permanent positions...............	$27,588,000	$27,635,000	+$47,000
Positions other than permanent....	7,457,000	7,468,000	+11,000
Other personnel compensation......	1,748,000	1,750,000	+2,000
Special personnel services........	3,346,000	3,350,000	+4,000
Subtotal, personnel compensation	40,139,000	40,203,000	+64,000
Personnel benefits.................	9,183,000	9,197,000	+14,000
Benefits for former personnel.......	40,000	40,000	---
Travel and transportation of persons	1,100,000	1,078,000	-22,000
Transportation of things............	172,000	167,000	-5,000
Rental payments to GSA..............	692,000	711,000	+19,000
Rental payments to others...........	451,000	464,000	+13,000
Communications, utilities and miscellaneous charges.............	1,390,000	1,429,000	+39,000

Budget Authority by Object -- continued

Printing and reproduction..........	$177,000	$171,000	-$6,000
Consultant services................	1,500,000	1,500,000	---
Other services.....................	10,074,000	9,333,000	-741,000
Purchases from government accounts..	25,073,000	25,719,000	+646,000
Operation of GOCOs.................	157,000	161,000	+4,000
R&D contracts......................	51,875,000	54,671,000	+2,796,000
Supplies and materials.............	6,635,000	6,423,000	-212,000
Equipment..........................	2,966,000	3,049,000	+83,000
Grants, subsidies & contributions...	369,168,000	388,548,000	+19,380,000
Total..............................	520,792,000	542,864,000	+22,072,000

National Institutes of Health
Administrative Costs
Budget Authority
NIAID

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	27,588	27,588	27,635	47
11.3	Other than full-time permanent	7,457	7,457	7,468	11
11.5	Other personnel compensation	1,748	1,748	1,750	2
11.8	Special personnel services payments	3,346	3,346	3,350	4
11.9	Subtotal, personnel compensation	40,139	40,139	40,203	64
12.1	Civilian personnel benefits	9,183	9,183	9,197	14
13.0	Benefits for former personnel	40	40	40	0
	Subtotal Pay Costs	49,362	49,362	49,440	78
21.0	Travel and transportation of persons	1,100	1,100	1,078	(22)
22.0	Transportation of things	172	172	167	(5)
23.2	Rental payments to others	451	451	464	13
23.3	Communications, utilities, and miscellaneous charges	1,390	1,390	1,429	39
24.0	Printing and reproduction	177	177	171	(6)
25.0	Other Services	35,946	33,143	33,101	(42)
26.0	Supplies and materials	6,635	6,635	6,423	(212)
	Subtotal non-pay costs	45,871	43,068	42,833	(235)
	Total Administrative Costs	95,233	92,430	92,273	(157)

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1994 House Report Virucides	
1. The House in its report 103-156, pages 59 and 60 stated -- "The Committee acknowledges the Institute's leadership in developing a research agenda on barrier methods for STD/HIV prevention.....The Committee encourages NIAID to mount a focused, sustained research effort to stimulate the development of safe, effective virucides."	1. In May 1993, NIH held a workshop on chemical barriers. As a result of that meeting, NIAID formulated a research agenda comprised of three parallel tracks aimed at the development of safe, effective topical microbicides: basic science, product development and clinical evaluation. In FY 1994, NIAID will establish program projects to foster multi-disciplinary basic research linking relevant disciplines such as microbiology, immunology, reproductive biology and toxicology, and cell biology. The NIAID contributed heavily to the NIH five year plan for research and development of topical microbicides that is to be incorporated into the PHS Initiative on Women Controlled Barrier Methods to Prevent STDs, HIV and Pregnancy. In mid-1994 NIAID will sponsor a second meeting on Topical Microbicides. This meeting will have a broader focus and will include the participation of commercial, academic, governmental and non-governmental agencies as well as advocacy groups. In FY 1995, NIAID plans to support a Topical Microbicide Cooperative Group, a multi-disciplinary research effort dedicated to defining the molecular basis of early steps in the infectious process for sexually transmitted pathogens, inflammatory response and mechanisms of interfering with the early host/parasite interactions.

Item	Action Taken or To Be Taken
1994 House Report	
Chronic Fatigue Syndrome	
2. The House in its report 103-156, page 60 stated -- "The Committee remains interested in efforts to discover the cause of and treatments for chronic fatigue syndrome, a disease that has disabled so many Americans. Within the increase provided, the Committee encourages the Institute to increase its efforts in this area."	2. The National Institute of Allergy and Infectious Diseases (NIAID) continues to support research on a broad front directed at understanding the underlying causes of Chronic Fatigue Syndrome (CFS) and to be responsive to opportunities suggested by new findings. The newly established Cooperative Research Centers provide a mechanism for expediting funding for pilot studies. Ongoing studies address many of the research priorities identified by constituency groups and the research community. During the past fiscal year, NIAID provided support to a new study that is involved in characterizing what may be a new human retrovirus. The virus was isolated from a patient with a syndrome compatible with the diagnosis of CFS. Another NIAID-supported researcher is studying chronic fatigue in Lyme disease patients who do not recover following prolonged antibiotic therapy. By concentrating on chronic fatigue as it relates to a specific illness, the investigator hopes to enhance our understanding of the factors that contribute to the development of CFS. Preliminary data indicate that in these patients chronic impairment is related to immunologic disturbances related to persistence of the infectious agent and/or its products. NIAID also made a New Investigator Research Award to a researcher undertaking a complex longitudinal study which includes identification of social factors and coping mechanisms

Item 1994 House Report	Action Taken or To Be Taken
	associated with CFS and the effects of depression on the disease course.
Lyme Disease	
3. The House in its report 103-156, page 60 stated -- "The Committee commends NIAID on its efforts in the development of direct tests for Lyme disease and encourages an expansion of resources devoted to applying these techniques in the investigation of the etiology of chronic Lyme disease and the appropriate treatment for it."	3. In the area of diagnostics, NIAID is currently supporting studies targeted to identifying borrelial epitopes responsible for protective cellular and humoral immune responses; to tracking spirochetal DNA in host tissues using PCR; to characterizing the major surface immunogens and develop ELISA assays to detect antibodies; and the recovery of borrelial nucleic acids from Lyme disease patients during various stages of disease. NIAID researchers at the Rocky Mountain Laboratories (RML) have demonstrated that membranous material shed by *B. burgdorferi* during growth may be useful as a diagnostic indicator of active infection and/or treatment effectiveness. Researchers continue to examine these materials with the aim of improving Lyme disease diagnostics. Finally, RML researchers have designed Polymerase Chain Reaction (PCR) primer sets which amplify all spirochete species associated with Lyme disease, and differentiate between these species. These sensitive and specific primers should allow for the rapid speciation of isolates and for improved clinical diagnosis of the disease. In the area of treatment research, NIAID supported extramural research on the role of gamma-interferon in the development of arthritis in chronic Lyme disease. Indications of a role for interferon or other cytokines in chronic stages of Lyme disease may suggest alternate or additional therapies. NIAID-supported investigators

Item

1994 House Report

Action Taken or To Be Taken

recently examined the cost-effectiveness of empirical, parenteral antibiotic treatment of patients with a positive serologic test for Lyme disease. They concluded that for most patients with a positive Lyme antibody titer whose only symptoms are nonspecific myalgia or fatigue the risk and costs of antibiotic therapy exceed the benefits. Only when the value of patient anxiety about leaving a positive test untreated exceeds the cost of such therapy is the empirical treatment cost-effective.

In FY 1994, NIAID plans to make awards in support of research on the immunology of Lyme disease, including efforts to: establish objective criteria for distinguishing chronic Lyme disease from other diseases; and delineate the role(s) of borrelial antigen variability, molecular mimicry and persistence of bacteria or antigens in chronic Lyme disease.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1994 Senate Report	
Microbicides	
1. The Senate in its report 103-143, page 92 stated -- "....The Committee believes that a focused, sustained research effort based on new funding is needed to stimulate the development of safe effective chemical barriers for women. Microbicide research should focus on a better understanding of early steps in infectious processes; identification, formulation, and preclinical evaluation of new preparations; clinical testing for safety and efficacy; and studies on acceptability and compliance of safe, effective microbicides."	1. Same response as number 1 in "1994 House Report", Virucides.
Asthma	
2. The Senate in its Report 103-143, pages 92 and 93 stated -- "....The Committee urges the Institute to give priority consideration to funding more basic asthma research and additional epidemiology studies, with emphasis on inner-city populations."	2. The cause, pathogenesis, diagnosis, treatment, and prevention of allergic diseases, such as asthma, are an important segment of the NIAID research portfolio. NIAID will continue to support basic research initiatives that explore the genetics of asthma, the roles of cytokines and adhesion molecules in hypersensitivity and inflammation reactions, and asthma as a T cell mediated disease. Our largest epidemiological study on asthma, the National Cooperative Inner-City Asthma Study (NCICAS), is now entering Phase II. In Phase I, baseline data for over 1,200 children with asthma, ages 4-9, in eight urban centers was collected. In Phase II, a common

Item	Action Taken or To Be Taken
1994 Senate Report	
	protocol, developed by a steering committee and seven scientific subcommittees, will be used and asthma severity will be assessed after a year of follow-up of each child. Results of the study are anticipated by the end of FY 1995.
Allergic Diseases	
3. The Senate in its report 103-143, page 93 stated -- "There is a particular need for additional basic research to increase our understanding of the chronic inflammatory response, which would enable researchers to develop innovative therapeutic interventions. We urge the Institute to provide more emphasis on this basic research if funds are available."	3. The cause, pathogenesis, diagnosis, treatment, and prevention of allergic diseases are an important segment of the NIAID research portfolio. NIAID scientists are exploring the potential use of interleukin-4 in reducing allergic reactions by reducing the cells that trigger allergic responses. In addition, NIAID Intramural researchers, using genetic engineering techniques, have produced mice that did not express IgE receptors on their mast cells. When injected with an allergen that binds to the IgE antibodies attached to these receptors, these mice did not go into anaphylactic shock -- a type of life-threatening allergic reaction. These results suggest that a drug that inactivates the IgE receptor on mast cells may prevent allergic reactions, including anaphylaxis. Within our extramural program, we are funding 11 Asthma, Allergy and Immunological Disease Research Centers. The Centers support basic and clinical research targeted to the mechanisms of allergic diseases, including asthma, in an effort to develop more effective therapies and methods for the prevention of allergic recognition, to identify the sequence of events in the development of the allergic response, and to isolate the environmental and host factors responsible for allergic diseases.

Item	Action Taken or To Be Taken
1994 Senate Report	
Tropical Infectious Diseases (TDRU)	
4. The Senate in its report 103-143, page 93 stated -- "....The Tropical Disease Research Units program is scheduled for renewal in 1994 and the Committee urges the Institute to make this renewal a priority."	4. The Tropical Disease Research Units are scheduled for renewal in FY 1995.
Chronic Fatigue Syndrome	
5. The Senate in its report 103-143, page 93 stated -- "....The Committee encourages the Institute to continue to expand research on Chronic Fatigue Syndrome. Studies that continue to look into retrovirus activity and other areas of infectious disease pathogenesis are strongly encouraged."	5. Same response as number 2 in "1994 House Report."

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amt. Authorized	1994 Appropriation	1995 Amt. Authorized	1995 Budget Request
Research and Investigation	Section 301	42§241	Indefinite--	$504,326,000	Indefinite--	$525,937,000
National Institute of Allergy and Infectious Diseases	Section 446	42§285f	Indefinite--		Indefinite--	
National Research Service Awards	Section 487	42§288-1	$400,000,000	16,466,000	Such Sums as Necessary	16,927,000
Total Budget Authority				520,792,000		$542,864,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1985	$325,379,000	$355,728,000[2]	$375,091,000	$368,528,000
1986	366,964,000	355,453,000[3]	412,965,000	366,964,000
1986 Sequester				-16,488,000
1987[4]	330,551,000	403,853,000	541,343,000	545,523,000
1988	551,102,000	439,667,000[5]	661,458,000	638,800,000
1989	435,084,000[6]	732,453,000[7]	758,352,000	744,152,000
1990	442,596,000[8]	845,523,000	847,112,000	843,745,000[9]
1990 Sequester				-10,768,000
1991	886,875,000	944,965,000	904,010,000	906,251,000[10]
1991 Sequester				-12,000
1992	976,711,000	972,830,000	965,952,000	959,914,000[11]
1993	1,010,845,000	990,055,000	989,055,000	979,471,000[12]
1994	1,065,583,000	1,065,583,000	1,065,583,000	1,065,583,000
1995	542,864,000[13]			

[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Excludes $8,690,000 in NRSA training programs not considered.

[3] Excludes $11,382,000 in NRSA training programs not considered.

[4] The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and appropriation spread the funding among the Institutes, including $145,850,000 for NIAID.

[5] Does not include funding for AIDS research. Consolidated at the Secretary's level.

[6] The 1989 request excludes funds for AIDS research ($310,268,000)

proposed for consolidation in the Office of the Assistant Secretary for Health.

7/ Excludes $13,537,000 in NRSA training programs not considered.

8/ The 1990 request excludes funds for the National HIV program ($400,116,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

9/ Excludes enacted administrative reduction of $2,573,000.

10/ Excludes enacted administrative reductions of $26,986,000.

11/ Excludes enacted administrative reductions of $11,197,000.

12/ Excludes enacted administrative reductions of $12,334,000.

13/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Offices of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Allergy, immunology and transplantation	---	$148,192	---	$153,565	---	$154,725	---	$154,669	---	$162,786	---	+$8,117
Microbiology and infectious diseases	---	235,714	---	259,866	---	267,861	---	267,924	---	281,983	---	+14,059
Subtotal.........	---	383,906	---	413,431	---	422,586	---	422,593	---	444,769	---	+22,176
Intramural research....	623	67,099	653	72,206	664	75,861	651	73,855	627	73,888	-24	+33
Research management and support..........	382	24,058	438	25,505	472	25,969	493	24,344	484	24,207	-9	-137
Total obligations......	1,005	475,063	1,091	511,142	1,136	524,416	1,144	520,792	1,111	542,864	-33	+22,072
Unobligated balance lapsing.............		---		---		113		---		---		---
Total, budget authority	1,005	475,063	1,091	511,142	1,136	524,529	1,144	520,792	1,111	542,864	-33	+22,072

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

Justification

National Institute of Allergy and Infectious Diseases

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
1,136	$524,529,000	1,144	$520,792,000	1,111	$542,864,000	-33	+22,072,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of Allergy and Infectious Diseases. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research."

The current era of unprecedented advances in biomedical research has increased expectations regarding the ability to prevent or cure previously uncontrollable diseases. However, the AIDS epidemic and the recent resurgence of tuberculosis (TB) demonstrate that society remains vulnerable to new and reemerging infectious diseases. In addition, more than 1 in every 10 Americans suffer from disorders of the immune system, including allergic diseases. Many of these life threatening or potentially debilitating diseases cause profound human suffering and place an enormous economic burden on patients and on the health care system.

Increased understanding of the microbes that cause human disease and the immune system that provides protection from these invaders is critical to preventing future infectious epidemics and to providing relief to individuals who already suffer from disease. Investment by the National Institute of Allergy and Infectious Diseases (NIAID) in these areas of basic and applied research provides an essential foundation for the development of vaccines to prevent disease, tests to diagnose disease, drugs to treat disease, and gene therapy to reverse disease.

The President's appropriation request of $542,864,000 for the NIAID represents current law requirements. No proposed law amounts are included. Funding for the NIAID research program during the last five years has been as follows:

	Amount	FTE
FY 1990	$438,098,000	919
FY 1991	475,063,000	1,005
FY 1992	511,142,000	1,091
FY 1993	524,529,000	1,136
FY 1994	520,792,000	1,144

Program Purpose and Method of Operation

Infectious diseases remain the most common cause of death for children worldwide, and disorders of the immune system are reported to affect more than 1 in every 10 Americans. The NIAID's mission is to conduct and support research and training aimed at alleviating suffering from these illnesses while reducing health care costs by developing approaches to prevent disease and halting the progression of disease to disability or death.

To accomplish this mission, NIAID supports research and training grants and contracts at many universities and medical centers in the United States and conducts basic and clinical investigations in its intramural laboratories located at Bethesda, Rockville, and Frederick, Maryland, and at Hamilton, Montana. The Institute's activities are carried out by three major research divisions: Allergy, Immunology, and Transplantation; Microbiology and Infectious Diseases; and Intramural Research.

Overall Budget Policy

The NIAID FY 1995 budget request is $542,864,000, an increase of $22,072,000 or 4.2 percent over the comparable FY 1994 level of $520,792,000. This request includes an increase of $5,000,000 targeted for tuberculosis research. The FY 1995 request will support 1,618 research project grants at $360,221,000 an increase of 36 awards and $18,585,000 over the FY 1994 Appropriation. NIAID will devote approximately 68 percent of its budget request to support research grants. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting grants portfolio, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific, justified program requirements and one time non-recurring costs such as equipment. Average costs of competing research project grants would receive an increase equal to the Biomedical Research Development Price Index (BRDPI) of 4.1 percent.

National Institute of Allergy and Infectious Diseases

Extramural Research

Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$422,699,000	$422,593,000	$444,769,000	+$22,176,000

The NIAID supports extramural research to control and prevent diseases caused by virtually all infectious agents through a wide spectrum of both basic and applied research projects such as studies of microbial physiology and antigenic structure, the development of diagnostic tests, and clinical trials to evaluate experimental drugs and vaccines. This kind of support offers hope for prevention, and ultimately eradication, of many diseases.

NIAID's Extramural Research Program also supports basic and clinical research to enhance our understanding of the causes and mechanisms that lead to the development of immunologic diseases and to generate an expanded knowledge base that may be applied to the development of improved measures of diagnosis, treatment, and prevention of a wide variety of immune system disorders such as allergies, autoimmune and genetic disorders, and organ transplantation rejection. Through outreach, demonstration, and education projects, NIAID supports the testing of the effectiveness of interventions to promote health and prevent disease in defined populations. NIAID's approach integrates the disciplines of basic science with relevant clinical specialties.

Funding for the NIAID Extramural Research program during the last five years has been as follows:

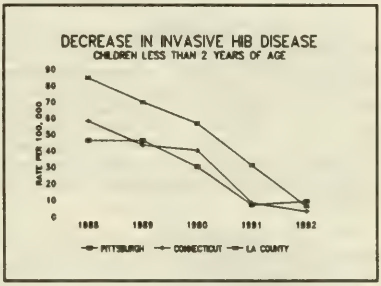
	Amount
FY 1990	$350,443,000
FY 1991	383,906,000
FY 1992	413,431,000
FY 1993	422,699,000
FY 1994	422,593,000

Rationale for the Budget Request

The FY 1995 budget request of $444,769,000 for the Institute's Extramural Research Program represents an increase of $22,176,000 or 5.2 percent above the FY 1994 level. Within the FY 1995 request level, funds are provided for the following budget activities: Allergy, Immunology and Transplantation in the amount of $162,786,000, an increase of $8,117,000 or 5.2 percent above the FY 1994 estimate of $154,669,000 and Microbiology and Infectious Diseases in the amount of $281,983,000, an increase of $14,059,000 or 5.2 percent above the FY 1994 estimate of $267,924,000. The following provides a brief overview of the research activities in these areas and describes some of the major research advances that will be capitalized on in FY 1995:

Investment in Basic Research. In FY 1995 NIAID will continue to foster its investment in basic research and to develop the essential foundation for future advances in immunology, infectious diseases, and vaccine development. The benefits of basic research has been demonstrated by our rapid response to AIDS and its pathogenic agent HIV. Basic research in immunology has contributed information on the immune system's response to infection, including the roles of antibodies and helper T cells. Research in microbiology and infectious diseases has provided fundamental knowledge that is facilitating the development of vaccines and drugs to treat diseases such re-emerging diseases as tuberculosis and childhood diseases such as Haemophilus influenza type b (Hib). NIAID and the National Institute of Child Health and Human Development invested heavily in the support of basic research studies that led to the highly successful Hib vaccines. This is truly an impressive accomplishment of which the NIH can be justifiably proud and which graphically illustrates the impact that basic research can have on an important health problem and on its solution.

The use of the conjugate Hib vaccines was recommended for universal use in infants in November of 1990. Last year we reported dramatic reductions in the rate of invasive Hib disease in infants, with a sharp fall in disease incidence in the year following licensure for young infants. The figure at the right illustrates the impact in three areas: Connecticut, Pittsburgh and Los Angeles. The 1992/1993 surveillance data indicate that this trend is continuing, with virtual eradication of this disease in some communities.



Re-emerging Microbes. The Institute of Medicine's Committee on Emerging Microbial Threats to Health recently reported that the threat posed by disease-causing microbes may be expected to continue and even intensify in coming years. One re-emerging microbe of recent public health concern has been the resurgence of *Mycobacterium tuberculosis* (M.tb). Although the elimination of this pathogen from the U.S. had been seen as an attainable goal, this objective was abruptly altered when the long-standing decline in the number of active cases of TB suddenly ended in 1984. Tuberculosis is a chronic disease that afflicts an estimated one third of the world's population, including an estimated 10 million people in the United States. M.tb causes more deaths worldwide than any other single infectious agent. It is estimated that there are 3.3 million tuberculosis deaths each year worldwide. Within the U.S. an estimated 15 million people have latent tuberculosis (TB) infections. The disease is both treatable and preventable and public health officials believe it can be eliminated by implementation of appropriate control programs. Yet, in many areas, including parts of the U.S., it is increasing. Several reasons have been identified for this public health failure including: effects of HIV infection on tuberculosis, increased movement of immigrants from countries where tuberculosis is common, and conditions associated with reactivation of latent disease such as poverty, homelessness, alcoholism, and drug abuse.

A vaccine is seen as the best preventative measure in combating *Mycobacterium tuberculosis*. In FY 1995, NIAID will initiate research studies for the purpose of enhancing the effectiveness of the immune system's response to intracellular, pathogenic organisms such as Mycobacteria spp, with particular emphasis placed on research targeting the stimulation of cytotoxic T cell attacks on infected cells.

Development of Microbicides. STDs are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with AIDS. In 1992 the estimated number of STD cases in the U.S. ranged between 9 and 11 million. In excess of five billion dollars in health care costs was spent to cure or treat these diseases. NIAID's research emphasis focuses on the development of vaccines and microbicides, and on clinical, epidemiologic, and behavioral investigations directed towards strategies for primary and secondary prevention of STDs and their sequelae--pelvic inflammatory disease, infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infection, and the spread of HIV.

In FY 1993 the NIAID, in collaboration with the National Institute of Child Health and Development, held a three day conference on the development of topical microbicides. These are intravaginal preparations that would be bactericidal and/or virucidal and used by women to prevent sexually transmitted infections. Preferably these could be formulated with or without spermicidal activity. The ideal products would have physical characteristics which render the microbicide "invisible" and amenable to use without partner knowledge or consent. The participants focused on a research agenda comprised of three parallel tracks: basic science, product development, and clinical evaluation.

Out of this conference, NIAID was able to define the basic science research agenda that it needed to develop effective virucides and bactericides and to delineate the nature of the required collaborations in cell biology, reproductive tract biology, pathology, and microbiology. In carrying out this agenda in FY 1995, NIAID is developing plans to enhance our existing efforts in the evaluation of antiviral and bactericidal products.

Introduction of Naked Genes that Encode Vaccines. In at least three laboratories genes have been isolated and employed experimentally as vaccines. The procedure involves isolating large molecules of DNA (genes) that carry the genetic code for a critical antigen (protein) that is a component of a potentially-pathogenic microorganism. When those molecules of DNA, i.e. genes, are introduced into an animal, some of them become integrated in cells of the animal where they initiate production of the antigen they encode. In this manner, the cells of the animal synthesize the antigen which then stimulates the immune system of the animal to recognize and reject any pathogens that display the same antigen. In other words, the naked genes have served as a vaccine to elicit protective immunity against the pathogen. In principal, this procedure can be extended to vaccination of humans against, at least some, pathogenic microorganisms. The great advantages in using DNA molecules as vaccines are, first, the ease with which they can be shipped and stored (dry) in parts of the world where refrigeration is not readily available and, second, the likelihood that only a single inoculation will be necessary to confer long-lasting immunity in human subjects. More research is necessary to determine how effective naked genes can be in human immunization and we plan to continue our ongoing efforts in this exciting new area.

Antigenized Antibodies as Vaccines. NIAID-supported investigators have recently devised a new way to prepare vaccines that promises to solve some of the difficulties of vaccinating against pathogenic microorganisms, such as tuberculosis and several sexually transmitted diseases. In many of these difficult cases, the antigens that are potentially useful for vaccines do not elicit vigorous immunity because they are not presented to the immune system properly and in sufficient quantity to stimulate immune responses. The new approach would utilize immunoglobulin molecules as conductors to insure that critical microbial antigens are introduced into antigen-processing and presenting cells (APC). The APC display a special affinity for binding and internalizing immunoglobulin molecules, and when the latter are coupled to a microbial antigen the antigen is also internalized and processed. The key peptides formed become localized on the surface of the APC where they are available to stimulate vigorous immune responses. This approach has worked exceedingly well in several recent studies in experimental animals and is likely to become a major technique in the development of vaccines in the very young and elderly who present special problems that complicate attempts to immunize them. NIAID will continue to support current efforts in this promising area of research in FY 1995.

Pertussis. NIAID has intensified its efforts to evaluate new acellular pertussis vaccines for licensure in the U.S., an essential component to the development of new multicomponent vaccines. In addition, a significant part of the NIAID research agenda supports advances in technologies and diseases with a high priority placed on the prevention of childhood morbidity and mortality, and with the potential of universal applicability within the pediatric immunization schedule. In FY 1995, NIAID will be evaluating the results of studies and clinical trials of NIAID's largest effort in the development of an efficacious and safe pertussis vaccine are anticipated to be available at the end of FY 1995. The field trials are being conducted in Sweden, Italy and Africa. The Swedish and Italian trials are testing four of the six acellular pertussis vaccines selected for further study by the NIAID Pertussis Task Force. A fifth vaccine is in an industry-sponsored trial in Senegal, and the sixth vaccine is being tested by NICHD at another site in Sweden.

The Children's Vaccine Initiative (CVI). CVI is a global program launched in 1990 at the World Summit for Children. The goals of the global program are to accelerate the transition to safe, affordable and heat stable vaccines that can protect children against the major infectious childhood killers with few doses given orally early in life, by facilitating the development, production, technology transfer, procurement and introduction of the new vaccines. The Global CVI, organized under an umbrella by WHO, UNICEF, UNDP, Rockefeller and the World Bank, have focused their emphasis on the following vaccines: heat stable oral polio, single dose tetanus vaccine, an improved measles vaccine for use in infants, pneumococcal vaccines, new Diphtheria-Tetanus-Pertussis vaccines and combinations which may include typhoid, hepatitis B, and others.

NIAID has been heavily involved in the attainment of that goal by developing and conducting field evaluations of four of six promising candidate acellular pertussis vaccines; developing and conducting phase I and II clinical evaluations of a pneumococcal glycoconjugate vaccine to protect infants against pneumonia and other invasive pneumococcal diseases; by establishing a new pediatric Vaccine Evaluation and Treatment Unit to evaluate the effects of mixing various combinations of Hib glycoconjugate vaccines in the primary series and immunizations; and in its support of a new Mucosal Immunization Research Group that is conducting studies of microencapsulation and other adjuvant technologies on the mucosal immune response, which will be important in developing effective oral vaccines and other vaccines that will provide protection against genito-urinary, gastrointestinal and respiratory tract infections. Continuing support to these efforts and the strides being made in the area of naked DNA and antigenized antibodies, as discussed above, will contribute to our vaccine development efforts in FY 1995.

Control of Aspirin-Induced Asthma. Aspirin-sensitive asthmatics are a subset of asthmatics who tend to have severe asthma even when not exposed to aspirin; they generally require oral steroids to control their asthma. NIAID investigators have used a new 5-LO inhibitor, zileuton, to completely block aspirin-induced asthma and nasal, gastrointestinal and skin responses to aspirin. These results strongly suggest (a) that LTC4 is the critical mediator of aspirin-sensitive asthma and (b) that the syndrome can be "cured" with specific inhibitors of 5-LO. It is thus possible that 5-LO inhibitors will be useful in treating aspirin-sensitive asthma and perhaps other patients with severe asthma. Ongoing studies will continue to be supported in FY 1995 to further clarify the role 5-LO inhibitors play in blocking asthmatic responses to aspirin-sensitive asthmatics.

Gene Causing X-Linked Agammaglobulinemia Found. Gene therapy is seen as the next scientific frontier to be exploited. Great strides continue to be made in identifying defective/missing gene-associated diseases on which the success of this new field depends. X-Linked Agammaglobulinemia (XLA) is an inherited, X-linked recessive immunodeficiency disease that occurs in male infants. It is characterized by an almost total absence of antibody and the cells that make it which results in recurrent bacterial infections. NIAID supported investigators have now identified the gene responsible for this disease. The gene encodes a protein termed B cell progenitor kinase (BPK) which is absent in the B lymphocytes of patients with XLA. Identification of this gene will facilitate the development of a test to identify infants with this disease while still in the womb and could possibly lead to treatment of the infant in the womb through gene therapy.

Inducing Tolerance With Donor Immune Tissue. Immunologic rejection is the major barrier to long term survival of transplanted organs. Graft loss means reduced quality or loss of life for the patient, and the need for re-transplantation puts an appreciable and potentially avoidable demand on the already inadequate supply of donor organs. New, improved immunosuppressive drugs and biologics have reduced the incidence of rejection and have improved graft survival significantly, particularly short term. However, these drugs and agents act in a non-specific manner and, in so doing, increase the danger of infection and cancer in the transplant patient.

NIAID is currently supporting a research protocol in which immune cells from the donor are used to turn off or "veto" the actions of recipient cells that recognize the donor. In ongoing studies funded by NIAID, researchers are characterizing the particular subset of cells responsible for the observed "veto" effect thus presenting the possibility that a few donor cells can be used to make patients specifically non-responsive to donors and eliminating the need for using toxic and potentially dangerous drugs. This procedure has been performed in an animal model and demonstrated the ability to extend the transplanted kidney's function indefinitely without the need for treatment with immunosuppressive drugs. NIAID plans to build on the results of this protocol which is opening up this exciting area. It is already felt that this research will one day give physicians the ability to provide organ replacement surgery which is less expensive, safer and more effective than that in current use.

National Institute of Allergy and Infectious Diseases

Intramural Research

Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
664	$75,861,000	651	$73,855,000	627	$73,888,000	-24	+$33,000

The Division of Intramural Research (DIR) conducts all of NIAID's in-house research program. NIAID researchers study allergic, immunologic and infectious diseases in the Division's 16 laboratories located in suburban Maryland at the main NIH campus in Bethesda with satellite laboratories in adjacent Rockville and Frederick and the Rocky Mountain Laboratories in Hamilton, Montana. The Bethesda facility also provides space for DIR's clinical activities at the NIH Clinical Center. Patients are frequently admitted to this clinical unit to participate in new and promising treatment or diagnostic procedures derived from the basic research that was conducted in the Division's laboratories.

Funding for the NIAID Intramural Research activity during the last five years has been as follows:

	Amount	FTE
FY 1990	$64,658,000	585
FY 1991	67,099,000	623
FY 1992	72,206,000	653
FY 1993	75,861,000	664
FY 1994	73,855,000	651

Rational for the Budget Request

The FY 1995 budget request for the Intramural Research budget activity is $73,888,000 an increase of $33,000 over the FY 1994 estimate. This request will provide funds for ongoing research in a wide variety of activities in patient health areas including asthma, allergy tuberculosis, sexually transmitted diseases, and the development of vaccines for major infectious diseases. The following are some of the research areas being supported in our Intramural Program:

Scientists Correct Three Different Forms of Chronic Granulomatosis Disease (CGD) *in vitro*. NIAID scientists have successfully treated three of four distinct forms of CGD in the laboratory by transferring the genes for missing proteins into blood precursor cells taken from CGD patients. CGD is a group of four distinct genetic disorders where all the patients appear to have the same clinical condition characterized by life-threatening recurrent infections. Normally the white blood cells which eat bacterial and fungi, the phagocytes, also kill the microorganisms by producing hydrogen peroxide. CGD phagocytes fail to produce hydrogen peroxide and have a defect in one of the proteins of the enzyme system (NADPH oxidase) responsible for hydrogen peroxide production. NIAID Scientists developed two *in vitro* model systems to demonstrate the feasibility of genetically correcting CGD. The first system uses a cell line of B-lymphocytes that have been transformed by Epstein-Barr virus (EBV-BL). EBV-BL from normal individuals produce small amounts of superoxide when stimulated, while those derived from CGD patients do not produce superoxide and are missing the oxidase component characteristic of that genetic form of CGD. In the second model system, scientists were able to induce marrow-like precursor cells harvested from the peripheral blood to proliferate and differentiate *in vitro* into mature neutrophils capable of superoxide production. Similar precursor cells from CGD patients could not produce superoxide, but introducing into them the MFG retrovirus containing the normal version of the specific CGD gene resulted in correction of superoxide production in 4 to 20 percent of resultant neutrophils. The findings from both systems show that it is possible to treat the disease using gene therapy. Theoretically, the peripheral blood progenitor model system of gene transfer could be scaled up to a procedure capable of being used for *in vivo* gene therapy for other disorders affecting bone marrow cells. Limited ongoing studies will explore the feasibility of this methodology in the coming fiscal year.

HSV-2 Protein Shows Potential as a Vaccine for Genital Herpes. The preliminary results from the first human studies of a genital herpes vaccine containing a genetically engineered protein from the herpes simplex virus type-2 show that the vaccine is safe and induces substantial immunity to the virus. This is the first study in which a vaccine was able to successfully treat a chronic infection. The work has implications for the treatment of genital herpes and for the development of therapeutic vaccines in general. Genital herpes is a very common sexually transmitted infection. Over 20 percent of adults Americans are infected, with a slightly higher rate in women than men. Within the past year, scientists vaccinated 98 individuals known to have genital herpes with the genetically engineered vaccine. The vaccination boosted the individuals' immunity to herpes simplex virus-2, and this was associated with a quarter to a third lower rate of recurrent infections than was seen in the subjects who were given placebo injections. The vaccine used in these first studies contained only one protein known as gD2, given along with a common, but relatively weak, immune adjuvant known as alum. In FY 1995 NIAID researchers will be investigating the benefits of adding a second virus protein called gD3 to the vaccine and using a more potent immune system-stimulating adjuvant known as MF59.

Biochemistry of Varicella Zoster Virus Unraveled. Intramural researchers have unraveled various biochemical properties of the protein "master switch" that turns varicella zoster virus (VZV) genes on and off. The finding will help scientists better understand the mechanisms by which VZV causes chicken pox (varicella), seen mostly in children, and shingles (zoster), seen in adults when VZV is reactivated from a dormant state. The master switch, a protein called IE62, is encoded by a gene called ORF62 in the virus. In molecular biology studies, the scientists established that IE62 regulates other genes and that it can also regulate the ORF62 gene promoter--a start signal for synthesizing RNA. This promoter, or start signal, is responsive to cyclic adenosine monophosphate, an abundant metabolite in both the neuronal and lymphocytic cells--cells that are the primary targets for VZV infection. The researchers have also found that the ORF62 gene promoter is highly active in neuronal cells and have mapped its affinity for neuronal cells to a specific region. The researchers also located the part of IE62 that activates the start signal and have partially characterized the factors in the infected cells that interact with IE62 to activate the virus genes. An understanding of the biochemical mechanisms by which IE62 controls gene expression in the virus may lead to the development of effective antiviral drugs and a safer vaccine.

Targeting IgE Receptors on Mast Cells May Be the Key to Preventing Allergic Reactions. Intramural scientists have demonstrated that drugs that block the immunoglobulin E (IgE) antibody receptor may prevent allergic reactions. Using genetic engineering techniques, the researchers produced mice that did not express this receptor on their mast cells, a type of connective tissue cell located around blood vessels and under mucus-secreting membranes in the respiratory and gastrointestinal systems. With both these genetically engineered mice and normal mice, the scientists then used a technique that causes mice to enter into anaphylactic shock when exposed to the appropriate antigen. Anaphylaxis is a life-threatening condition in which an ordinarily innocuous antigen called an allergen binds to IgE antibodies that are themselves attached to IgE receptors on the surface of mast cells. The allergen binding induces the mast cells to release chemicals such as histamine. These chemicals cause difficulty in breathing because they induce constriction of the larynx and bronchi, and they also cause shock because of their effects on the cardiovascular system. These effects include vasodilation and the exudation of plasma out of blood vessels, resulting in a drastic fall in blood pressure. The researchers found that the mice without IgE receptors on their mast cells did not enter into anaphylactic shock, unlike the normal mice. This suggests that drugs that inactivate the IgE receptor on mast cells may prevent allergic reactions, such as anaphylaxis. NIAID will use the information from this project to explore this theorem.

Hepatitis E Test Identifies Cause of Hepatitis Epidemics in India and Pakistan. NIAID researchers have developed a sensitive and specific test to detect hepatitis E virus, a newly identified strain of hepatitis virus. Using this test, the researchers have shown that this strain has in fact been responsible for the many viral hepatitis epidemics that have occurred in India and Pakistan over the last three decades. Last year, the research team found that the newly identified strain of hepatitis E virus from Pakistan causes viral hepatitis in a number of different monkey species. After identifying the new strain, scientists sequenced its genome and, using molecular biology techniques, produced large amounts of a viral protein that reacts with antibodies induced by hepatitis E infection. This synthetic viral protein was used to develop the diagnostic assay for detecting hepatitis E infection. When scientists injected monkeys with the protein, they found that the animals developed a good antibody response to the infecting virus. In FY 1995 NIAID researchers plan to evaluate the synthetic viral protein as a candidate vaccine in appropriate animal models.

Mutation in Mice May Lead to Improved Treatment of Immunodeficiency Diseases. NIAID intramural scientists identified a mutation in mice that may lead to the detection of a new class of immunodeficiency diseases in humans. The discovery will also allow the scientists to investigate the genetic mechanisms underlying X-linked agammaglobulinemia, an immunodeficiency that renders infants highly susceptible to bacterial infections. The researchers discovered the mutation on the X chromosome in a gene that is important for the development of B lymphocytes, the cells that produce antibodies. The investigators found that the mice carrying this mutated gene possessed fewer antibodies in their blood and only half the number of B lymphocytes as normal animals. A similar mutation in a comparable gene on the X chromosome is responsible for X-linked agammaglobulinemia in humans, but the immunodeficiency in humans is considerably worse than in mice. Patients have almost no antibodies because B cell development is completely lacking. The scientists found that both the mouse gene and the human gene code for the production of an enzyme that participates in B cell development. However, the mutation in mice has less severe manifestations than the one in humans because it is in a different part of the gene and causes less disruption to the activity of the enzyme. The researchers speculate that there may be relatively mild immunodeficiencies in humans caused by mutations that are similar to the one found in mice. This suggests that if a physician was aware that a patient had this type of abnormality, he or she might pursue the treatment of infections in this patient more aggressively.

Malaria Parasite Cell Lines Help Scientists Identify Potential Drug Targets. Intramural scientists have developed four auxotrophic lines of malaria parasites that require a supplemental nutrient to grow. Auxotrophs are mutants that are unable to synthesize a key molecule in metabolism and therefore require this molecule added to their culture medium. By helping scientists discover the components of parasite metabolism, auxotrophs facilitate the search for new drug targets. The scientists developed auxotrophic lines of *Plasmodium falciparum*, one of the protozoal parasites that cause malaria. These auxotrophs require para-aminobenzoic acid (PABA), one of the B vitamins. The development of these auxotrophs substantiates that *P. falciparum* synthesizes PABA and that a drug that blocks a key step in the PABA synthetic pathway may be effective in killing the parasite. The researchers also suggest that auxotrophs may be useful in developing a malaria vaccine, much as the use of auxotrophic mutants of the bacteria *Salmonella* has led to a new generation of salmonella vaccines. An appropriate auxotrophic mutant would have all of the antigens of the normal organism, but would be sufficiently weakened that it would not cause disease when injected. Information gained from these studies will aid in the development of new drugs against malaria.

Scientists Find Potential Carriers of "Insecticide" Genes. NIAID researchers have identified some of the microbes eaten by the larvae of *Anopheles gambiae*, the mosquito species primarily responsible for the transmission of the malaria parasite in sub-Saharan Africa. The goal of the project is to identify organisms that might serve as carriers of "insecticide" genes, whose products would kill the mosquito larvae and prevent the spread of malaria. The researchers have found that the larvae are more likely to eat bacteria whose cell surfaces are hydrophilic, or have a strong affinity to water. The bacteria with cell surfaces that are hydrophobic (lack affinity to water) are difficult to digest. Studies with mutants have shown that bacteria can be made more or less digestible by altering the water affinity of their cell surfaces. The researchers have also determined the structure of a certain gene in a number of bacterial species, which should help in the development of molecular probes for the rapid characterization of the microbes in the larval mosquito habitat. The current method involving antibody probes is slower and less sensitive. To date, over 150 strains of microorganisms have been collected and purified from various larval breeding sites in Mali, a country in western Africa. Of these, over 80 have been identified to at least the genus level. Identifying the microbial inhabitants of larval breeding sites will help in determining which species are ingested by the larvae and thus which ones might be good candidates for carrying "insecticide" genes. NIAID plans to continue its efforts in this area in FY 1995.

Studies of Immune Response to Filarial Infections May Lead to Preventive Therapies. Some individuals who are infected with filarial worms develop diseases, such as lymphatic filariasis or onchocerciasis, whereas others do not develop symptoms even though the worms remain within their bodies. Intramural scientists have discovered that individuals who develop disease after filarial infection mount a type of immune response termed Th1, whereas those who do not manifest disease despite infection have a different type of immune response, termed Th2. Th1 and Th2 refer to two different classes of immune cells called helper T lymphocytes. Th1 cells secrete a set of messenger chemicals that cause other immune cells to attack the worms. However, in the case of filarial infections, the accumulation of immune cells cause the symptoms of disease, such as the lymph flow obstruction that occurs in lymphatic filariasis. Th2 cells secrete another set of chemicals that stimulate the production of antibodies against the worms. The antibodies bind to antigens on the worms, thereby signalling various enzymes and immune cells to attack them. In filarial infections, this response appears to contain the worms while not causing the symptoms of disease. The researchers have found that the messenger chemicals interleukin-10 and transforming growth factor-beta can enhance the Th2 response and suppress Th1, suggesting that therapies that stimulate the production of these chemicals may be effective in preventing disease due to filarial infections. With an understanding of the mechanisms behind these immune responses, scientists might be able to design therapies that would augment the Th2 response over Th1, thus preventing people from developing disease even if they are infected. The researchers have also identified a gene that appears to predispose individuals to developing disease upon filarial infection. Testing for the presence of this gene might identify individuals who are most likely to benefit from preventive therapy. NIAID plans to continue its efforts in this area.

National Institute of Allergy and Infectious Diseases

Research Management and Support

Authorizing Legislation - Section 301, 446, and 487 of the Public Health Service Act.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
472	$25,969,000	493	$24,344,000	484	$24,207,000	-9	-$137,000

The Research Management and Support (RMS) activity provides the resources that contribute to the overall management and policy direction of the Institute's extramural programs. The managerial, scientific, and administrative functions encompassed by this activity includes grants and contracts management, the scientific review of grant and contract applications, scientific program management, financial management, program planning and development, personnel, information dissemination, data management, procurement, property, and technology transfer.

Funding for the Research Management and Support activity during the last five years has been as follows:

	Amount	FTE
FY 1990	$22,997,000	334
FY 1991	24,058,000	382
FY 1992	25,505,000	438
FY 1993	25,969,000	472
FY 1994	24,344,000	493

Rationale for the Budget Request

The FY 1995 NIAID budget request for the Research Management and Support budget activity is $24,207,000, an decrease of $137,000 from the 1994 estimate.

In FY 1995, NIAID management will continue in its efforts to reassess the state of science in those areas within the Institute's purview. These efforts will include the review of progress and the identification of areas of unusual scientific opportunity which may lead to new approaches to support and facilitate research. Vital to these efforts are the continued participation in, and sponsorship of selected meetings, conferences, workshops, and symposia on high-priority research topics and issues, including areas of technology transfer and consensus development. These activities provide the necessary forum to exchange and foster new information, and to translate research findings to clinical care.

NIAID will draw upon the advice and counsel of its task forces, national advisory groups, blue ribbon panels and other outside experts in the development and refinement of the Institute's scientific agenda. This methodology was proven to be extremely beneficial in the development of the NIAID Tuberculosis Agenda and the Vaccine Development Initiatives Plan.

Emphasis will continue to be placed on outreach activities directed to health professionals, voluntary associations and various private sector groups that extend to lay audiences or at-risk groups. The Institute will also continue to work closely with minority professional associations, medical facilities and academic institutions in the dissemination of information on the diseases and disorders that disproportionately affect minority populations; encourage young minority scientists to participate in the Institute's scientific mission; and to reach out to the minority scientists of tomorrow through its several student programs.

National Institute of Allergy and Infectious Diseases
Detail of Full-Time Equivalent Employment (FTE)

	FY 1993 Actual	FY 1994 Estimate	FY 1995 Estimate
Office of the Director.......	154	171	169
Division of Intramural Research..................	664	651	627
Division of Extramural Activities................	110	110	108
Division of Allergy, Immunology, and Transplantation..........	21	22	21
Division of Acquired Immunodeficiency Syndrome..	131	133	131
Division of Microbiology and Infectious Diseases....	56	57	55
TOTAL NIAID.............	1,136	1,144	1,111

Average GS/GM Grade

1990	9.5
1991	10.0
1992	10.1
1993	10.0
1994	10.0
1995	10.0

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

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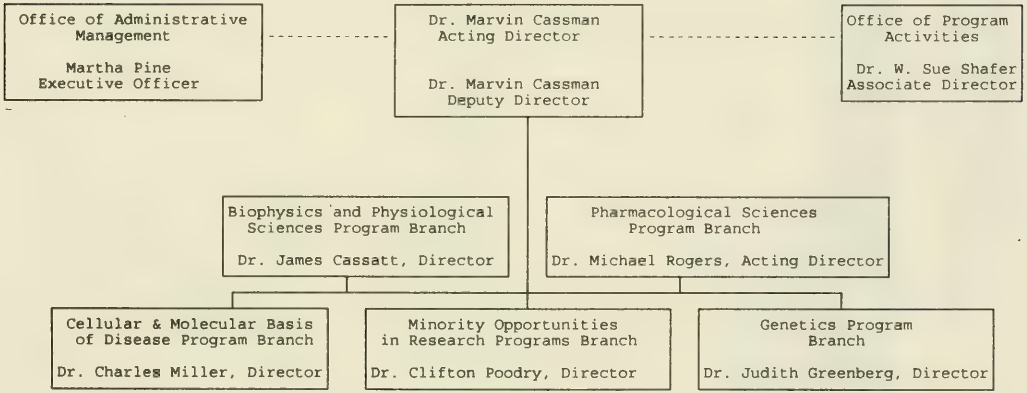
National Institute of General Medical Sciences

Organization Structure


Office of Administrative Management
Martha Pine
Executive Officer
Dr. Marvin Cassman
Acting Director
Dr. Marvin Cassman
Deputy Director
Office of Program Activities
Dr. W. Sue Shafer
Associate Director
Biophysics and Physiological Sciences Program Branch
Dr. James Cassatt, Director
Pharmacological Sciences Program Branch
Dr. Michael Rogers, Acting Director
Cellular & Molecular Basis of Disease Program Branch
Dr. Charles Miller, Director
Minority Opportunities in Research Programs Branch
Dr. Clifton Poodry, Director
Genetics Program Branch
Dr. Judith Greenberg, Director

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For carrying out section 301 and Title IV of the Public Health Service Act with respect to general medical sciences, [$875,511,000] *$882,189,000 of which, $9,502,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriation Act, 1994.)*

National Institute of General Medical Sciences

Language Analysis

Language Provision	Explanation
".....of which, $9,502,000 shall not become available for obligation until September 19, 1995."	*To ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.*

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National Institute of General Medical Sciences

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation.....................	$839,804,000	$875,511,000	$882,189,000
Section 511 reduction............	-6,718,000	---	---
Section 513 Cons. Serv. reduction.	-91,000	---	---
Section 216 S & E reduction.......	-414,000	---	---
Subtotal, adjusted appropriation................	832,581,000	875,511,000	882,189,000
Real transfer to: NIAID for tuberculosis research.......................	-346,000	---	---
Comparative transfer to: Office of AIDS research for HIV activities.............	-16,850,000	-23,945,000	---
Subtotal, adjusted budget authority....................	815,385,000	851,566,000	882,189,000
Unobligated balance lapsing.......	-44,000	---	---
Total, Obligations..............	815,341,000	851,566,000	882,189,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1993--$17,410,000; FY 1994--$20,000,000; FY 1995--$20,000,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Mechanism

	1993 Actual		1994 Estimate		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	2,571	$505,278,000	2,533	$526,097,000	2,153	$455,262,000
Admin. supplemental	(119)	969,000	(120)	1,079,000	(120)	1,122,000
Competing						
Renewal	418	97,470,000	401	97,428,000	696	171,415,000
New	345	49,973,000	356	53,836,000	489	76,487,000
Supplemental	5	722,000	4	379,000	10	1,780,000
Subtotal, competing	768	148,165,000	761	151,643,000	1,195	249,682,000
Subtotal, research projects	3,339	654,412,000	3,294	678,819,000	3,348	706,066,000
Research Centers						
Pharmacological sciences	2	1,930,000	2	2,012,000	2	2,095,000
Anesthesiology	1	868,000	1	904,000	1	941,000
Trauma and burn	6	4,936,000	6	5,142,000	6	5,353,000
Subtotal research centers	9	7,734,000	9	8,058,000	9	8,389,000
Other research						
Research career program	21	1,271,000	21	1,271,000	21	1,306,000
MBRS	98	32,795,000	98	34,795,000	103	36,535,000
Other	73	3,271,000	71	3,275,000	85	4,000,000
Subtotal, other research	192	37,337,000	190	39,341,000	209	41,841,000
Total, research grants	3,540	699,483,000	3,493	726,218,000	3,566	756,296,000

Training:						
Individual awards						
Noncompeting	327	7,647,000	408	10,203,000	454	11,794,000
Competing	222	5,148,000	235	6,064,000	189	4,473,000
Subtotal, individual	549	12,795,000	643	16,267,000	643	16,267,000
Institutional awards						
Noncompeting	2,911	62,208,000	2,911	65,217,000	2,381	55,160,000
Competing	564	12,528,000	608	13,268,000	1,138	23,325,000
Subtotal, institutional	3,475	74,736,000	3,519	78,485,000	3,519	78,485,000
Total, training	4,024	87,531,000	4,162	94,752,000	4,162	94,752,000
Research and development contracts	5 FTEs	1,847,000	7 FTEs	2,757,000	7 FTEs	2,877,000
Intramural research	19	1,180,000	19	1,158,000	17	1,105,000
Research management and support	172	25,344,000	169	26,681,000	167	27,159,000
TOTAL	191	815,385,000	188	851,566,000	184	882,189,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Summary of Changes

1994 Estimated budget authority	$851,566,000
1995 Estimated budget authority	882,189,000
Net change	+30,623,000

Changes:	1994 Current Estimate Base FTEs	1994 Current Estimate Base Budget Authority	Change from Base FTEs	Change from Base Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increases		$830,000		+$12,000
b. Annualization of pay raise		830,000		+10,000
c. One less day of pay		830,000		-3,000
d. FY 1995 pay increase		830,000		+11,000
e. Centrally furnished services		313,000		+13,000
Subtotal				+43,000
2. Research Management & Support				
a. Within grade increases		9,890,000		+145,000
b. Annualization of pay raise		9,890,000		+117,000
c. One less day of pay		9,890,000		-38,000
d. FY 1995 pay increase		9,890,000		+132,000
e. Centrally furnished services		7,622,000		+622,000
f. FECF unemployment compensation		54,000		+8,000
g. Working capital fund increase		782,000		+6,000
h. FTS increase		51,000		+3,000
i. Service and supply fund increase		4,830,000		+135,000
j. Inflationary increase		9,169,000		+122,000
Subtotal				+1,252,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	2,533	527,176,000	-380	-70,792,000
b. Competing	761	151,643,000	+434	+98,039,000
Subtotal	3,294	678,819,000	+54	+27,247,000

2. Centers	9	$8,058,000	---	+$331,000
3. Other Research:				
a. Research career program	21	1,271,000	---	+35,000
b. MBRS program	98	34,795,000	+5	+1,740,000
c. Other research	71	3,275,000	+14	+725,000
Subtotal			+19	+2,500,000
4. Research and development contracts	7	2,757,000	---	+120,000
	FTEs		FTEs	
5. Intramural:				
a. Admin. cost reduction and Reduction of FTEs	19	1,158,000	-2	-96,000
6. Research Management & Support:				
a. Admin. cost reduction and Reduction of FTEs	169	26,681,000	-2	-774,000
Subtotal			---	+29,328,000
Total changes			-4	+30,623,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object

	1994 Estimate	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	188	184	-4
Full-time equivalent of overtime and holiday hours.......	1	1	---
Average SES salary..................	$110,701	$112,030	+$1,329
Average GS grade....................	10.1	10.1	---
Average GS salary...................	31,573	31,952	+379
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$58,074	$61,678	+3,604
Average salary of ungraded positions.	$43,684	$45,353	+1,669
Personnel compensation:			
Full-time permanent...............	7,631,000	7,760,000	+129,000
Other than full-time permanent.....	1,046,000	1,010,000	-36,000
Other personnel compensation.......	219,000	222,000	+3,000
Special personal services payments.	4,000	3,000	-1,000
Subtotal, personnel compensation.	8,900,000	8,995,000	+95,000
Personnel benefits..................	1,812,000	1,881,000	+69,000
Benefits for former personnel........	8,000	8,000	---
Travel and transportation of persons.	273,000	272,000	-1,000
Transportation of things.............	49,000	67,000	+18,000
Rental payments to others............	12,000	12,000	---
Communications, utilities, and miscellaneous charges............	271,000	279,000	+8,000
Printing and reproduction............	290,000	272,000	-18,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object--continued

	1994 Estimate	1995 Estimate	Increase or Decrease
Other services:			
Consulting services	516,000	671,000	+155,000
Other services	135,000	135,000	---
Purchases from govt. accts	15,056,000	15,166,000	+110,000
R&D contracts	2,371,000	2,491,000	+120,000
Supplies and materials	140,000	130,000	-10,000
Equipment	763,000	762,000	-1,000
Grants, subsidies, and contributions	820,970,000	851,048,000	+30,078,000
Total	851,566,000	882,189,000	+30,623,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIGMS

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	7,631	7,631	7,760	129
11.3	Other than full-time permanent	1,046	1,046	1,010	(36)
11.5	Other personnel compensation	219	219	222	3
11.8	Special personnel services payments	4	4	3	(1)
11.9	Subtotal, personnel compensation	8,900	8,900	8,995	95
12.1	Civilian personnel benefits	1,812	1,812	1,881	69
13.0	Benefits for former personnel	8	8	8	0
	Subtotal Pay Costs	10,720	10,720	10,884	164
21.0	Travel and transportation of persons	273	273	272	(1)
22.0	Transportation of things	50	49	67	18
23.2	Rental payments to others	20	12	12	0
23.3	Communications, utilities, and miscellaneous charges	271	271	279	8
24.0	Printing and reproduction	290	290	272	(18)
25.0	Other Services	15,594	11,285	11,550	265
26.0	Supplies and materials	143	140	130	(10)
	Subtotal non-pay costs	16,641	12,320	12,582	262
	Total Administrative Costs	27,361	23,040	23,466	426

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Significant Items in the House, Senate, and Conference Appropriations Committee Reports

Item	Action Taken or to be Taken:
1994 House Report	
1. Minority Opportunities in Research Programs: In its House Report 103-156, page 61, stated: "The Committee encourages the NIGMS to increase funding for these programs due to their longstanding success in training minorities in biomedical research and other scientific research projects."	1. In fiscal year 1994, the Institute has increased funding for the Minority Access to Research Careers (MARC) Program by 14.2% over the fiscal year 1993 and for the Minority Biomedical Research Support (MBRS) Program by 6.1%. In addition, funding for the National Predoctoral Fellowships for Minorities will be increased by 88.1%.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amt. Authorized	1994 Appropriation	1995 Amt. Authorized	1995 Budget Request
Research and Investigation.........	Section 301	42 241	Indefinite		Indefinite	
National Institute of General Medical Sciences..............	Title IV, Part Section 453	42 285h 288c	Indefinite	$756,814,000	Indefinite	$787,437,000
National Research Service Awards.........	Section 487 (d)	42 288	$400,000,000	94,752,000	such sums as necessary	94,752,000
Total Budget Authority.				851,566,000		882,189,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$458,484,000	$455,593,000 2/	$510,872,000	$514,765,000
1986 Sequester	---	---	---	-22,135,000
1987	471,533,000	576,562,000	565,271,000	570,916,000
1988	482,004,000	666,037,000 3/	650,617,000	632,676,000
1989	676,728,000 4/	623,087,000 5/6/	690,653,000 5/	690,653,000
1990	766,421,000 7/	692,639,000 8/	752,939,000 9/	691,278,000 10/
1990 Sequester	---	---	---	-9,496,000
1991	745,494,000 8/	693,499,000 11/8/	779,351,000 8/	760,010,000 12/
1991 Sequester	---	---	---	(10,000)
1992	833,180,000	820,160,000	815,158,000	818,910,000 13/
1993	862,069,000	833,807,000	824,529,000	832,581,000 14/
1994	833,064,000	875,511,000	875,511,000	875,511,000
1995	882,189,000 15/			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Excludes $57,721,000 in NRSA training programs not considered.

3/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

4/ Does not include funding for AIDS research ($11,100,000). Proposed for consolidation at the Office of the Assistant Secretary for Health.

5/ Includes $11,100,000 for AIDS research.

6/ Excludes $69,841,000 in NRSA training programs not considered.

7/ Excludes funds for AIDS research proposed for consolidation in the Office of the Assistant Secretary for Health. Includes funds for the Human Genome Research Initiative.

8/ Includes funds for AIDS research and the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources. Excludes funds for the Human Genome Research Initiative to be considered under a separate new appropriation account.

9/ Includes funds for AIDS research and funds for the Human Genome Research Initiative.

10/ Includes funds for AIDS research. Excludes funds for the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources, the Human Genome Research Initiative and an enacted administrative reduction of $588,000.

11/ Excludes $85,650,000 in NRSA training programs not considered.

12/ Excludes enacted administrative reductions of $19,240,000 and funds transferred from other accounts for the Shannon awards.

13/ Excludes enacted administrative reductions of $1,276,000 and a rescission of $790,000.

14/ Excludes enacted administrative reductions of $7,224,000.

15/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Estimate		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural research												
Cellular and molecular basis of disease....	---	$209,037	---	$223,759	---	$230,792	---	$244,721	---	$253,541	---	$8,820
Genetics.............	---	214,872	---	228,335	---	227,480	---	232,836	---	241,598	---	8,762
Pharmacology and Biorelated Chemistry..	---	108,764	---	118,899	---	123,403	---	126,674	---	130,649	---	3,975
Biophysics and physiological sciences....	---	139,614	---	153,186	---	159,432	---	166,347	---	171,701	---	5,354
Minority opportunities in research:												
Minority biomedical research support..	---	31,614	---	33,190	---	32,795	---	34,795	---	36,535	---	1,740
Minority access to research careers..	---	13,220	---	13,514	---	13,103	---	14,966	---	15,714	---	748
Special minority initiatives.......	---	1,392	---	1,617	---	1,856	---	3,388	---	4,187	---	799
Subtotal...........	---	46,226	---	48,321	---	47,754	---	53,149	---	56,436	---	3,287

Intramural research...	18	1,080	19	1,109	19	1,176	19	1,158	17	1,105	-2	-53
Research management and support.........	166	22,576	173	24,950	172	25,304	169	26,681	167	27,159	-2	478
Total Obligations...	184	742,169	192	798,559	191	815,341	188	851,566	184	882,189	-4	30,623
Unobligated balance lapsing.............		52		47		44		---		---		---
Total, Budget Authority.........	184	742,221	192	798,606	191	815,385	188	851,566	184	882,189	-4	30,623

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of General Medical Sciences

FY 1993 Actual		FY 1994 Estimate		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
191	$815,385,000	188	$851,566,000	184	$882,189,000	-4	+$30,623,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of General Medical Sciences (NIGMS). Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

The NIGMS is the component of the National Institutes of Health (NIH) that is devoted to the support of basic biomedical research. Its programs are not targeted to specific diseases, life stages, or environmental factors. Rather, NIGMS grantees work to solve the most fundamental mysteries of life, using the approaches of structural biology, biophysics, genetics, cell and molecular biology, chemistry, and pharmacology. Their discoveries find broad applications in medical treatments, diagnostic tests, cures, and preventive measures, both directly and through the biotechnology and pharmaceutical industries.

The advances reported by NIGMS-supported scientists are often incremental and are usually highly technical. It may not seem earth-shaking to a nonscientist to learn that mutant yeast and bacteria are unable to repair errors that occur during the copying of their genetic material. But basic research in this very area--conducted by Dr. Richard Kolodner of the Dana-Farber Cancer Institute in Boston, Dr. Paul Modrich of Duke University, and their colleagues--contributed to the exciting discovery of the gene that is defective in a common form of colon cancer. This finding is expected to lead, in a matter of months, to a test that will tell people with a family history of such cancer whether they have inherited the defective gene. Those who have the gene will be advised to undergo regular preventive screening, and those who have not inherited the gene will be spared the anxiety associated with being at increased risk for colon cancer.

Similarly, years of NIGMS-supported basic research on molecules that remove a harmful form of oxygen from cells placed scientists in an ideal position to capitalize on a discovery in an unrelated field--amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease. When it was reported in early 1993 that ALS is linked to a defect in superoxide dismutase, the enzyme that removes the harmful oxygen molecules from cells, scientists could draw upon the body of knowledge about the structure and function of this enzyme that has been amassed since the 1960's. Because of the ready availability of detailed information on superoxide dismutase, prospects are good for improved diagnosis, genetic counseling, and possible preventive treatments or gene therapy for ALS.

As these examples show, basic research is indeed the foundation for more targeted, disease-oriented studies. It is not always possible to predict which areas of research will be the most fruitful or which will be effective in addressing a specific biomedical problem, but scientists are trained to spot where breakthroughs are likely to occur. For this reason, fundamental research on the underlying mechanisms that drive the activities of molecules, genes, cells, organs, and organisms holds the greatest promise for providing solutions to today's biomedical problems, as well as those that will present themselves in the future. As the late Dr. Lewis Thomas, who has been called the "poet laureate" of science, observed in The Medusa and the Snail: "There is a very high probability that whatever astonishes us in biology today will turn out to be usable, and useful, tomorrow."

To increase the chances that it will support investigations that are truly innovative and that will lead to future breakthroughs, NIGMS recently initiated a program to fund research in new and underexamined areas of science. Applications funded under this program will be those that promise unusually significant results and insights, but that have elements of risk that may compromise their likelihood of success. By funding such applications, NIGMS will ensure a greater degree of diversity in its grant portfolio.

Training New Scientists: Just as basic biomedical research is an investment in the future, so too is the training of new scientists. NIGMS has long played a major role in this endeavor. Many NIGMS training programs are multidisciplinary in nature, because it is this sort of broad exposure that will enable tomorrow's scientists to capitalize on new research findings and move rapidly in new directions.

In addition to its general training programs in the fields in which it supports research, NIGMS also has several special training activities in areas that have critical shortages of well-trained scientists. These areas include biotechnology, molecular biophysics, and the chemistry-biology interface. The latter two areas support training with particular relevance to AIDS and tuberculosis by producing scientists who are well-positioned to identify new approaches to the design of drugs to fight these diseases.

The Institute's Medical Scientist Training Program supports students who plan to combine basic research and clinical investigation. These individuals are exceptionally qualified to translate basic findings into medical advances. A 1993 graduate of this program, Dr. Matthew Anderson, was a member of the research team at the University of Iowa that determined the mechanism by which a defective protein causes cystic fibrosis. His doctoral dissertation on this work won both university and national awards.

Increasing the Number of Minority Scientists: Perhaps the personnel shortage area in science that is of greatest concern is the underrepresentation of people from certain minority groups. NIGMS works to remedy this underrepresentation through the activities of its Minority Opportunities in Research Programs Branch. This branch--which includes the Minority Biomedical Research Support (MBRS) and Minority Access to Research Careers

(MARC) Programs--supports research at institutions with substantial minority enrollments, the research training of minority students and faculty at minority-serving institutions, and related programs that enrich these institutions' science curricula and research environments.

The President's appropriation request of $$882,189,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of General Medical Sciences during the last five years has been as follows:

	Amount	FTE
FY 1990	$691,256,000	173
FY 1991	742,221,000	184
FY 1992	798,606,000	192
FY 1993	815,385,000	191
FY 1994	851,566,000	188

Purpose and Method of Operation

NIGMS places major emphasis on the support of individual, investigator-initiated research grants. It funds a limited number of research centers in selected fields--such as trauma and burn research and the pharmacological sciences (including anesthesiology)--in which the interaction of basic and clinical researchers is critical for rapid scientific progress.

NIGMS also funds several research contracts that provide important resources for basic scientists. In research training, the Institute supports a large portfolio of both individual fellowship awards and institutional training grants. Some of these training programs help meet personnel shortages in rapidly expanding fields of science, such as biotechnology, or promote the access of individuals from minority groups to biomedical research careers.

Overall Budget Policy

The NIGMS budget request for FY 1995 continues to emphasize basic biomedical research studies through the support of investigator-initiated research project grants. The budget request is $882,189,000, which represents an increase of 3.6 percent over the FY 1994 estimate. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting components, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The request will support 1,195 competing research project grants and 2,153 noncompeting research project grants. The increase of 434 competing grants over FY 1994 is due to a greater than usual number of expiring grants becoming eligible as competing renewals in FY 1995. This increase in competing grants is offset by a corresponding decrease of 380 noncompeting grants, which are terminating during FY 1994. The FY 1995 budget request will fund 9 research centers, 21 research career awards, 103 Minority Biomedical Support (MBRS) awards, 85 other research projects, and 7 research and development contracts. This represents the same number of research centers, research career awards, and research and development contracts that were funded in 1994; and an increase of 5 MBRS awards and 14 other research projects over 1994.

In 1995, approximately 4,162 research trainees will be supported. Although this level represents the same total number of research trainees that were funded in 1994, a 5 percent increase will be provided for minority research training programs.

Included in this request are administrative reductions and full-time equivalent (FTE) reductions for both Intramural Research and Research Management and Support. The request will provide 184 FTEs, a decrease of 4 FTEs from the FY 1994 level.

EXTRAMURAL RESEARCH PROGRAM

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual	FY 1994 Estimate	FY 1995 Estimate	Increase or Decrease
$788,861,000	$823,727,000	$853,925,000	+$30,198,000

Rationale for the Budget Request

The FY 1995 budget estimate for the Extramural Programs is $853,925,000, an increase of 3.7 percent over the FY 1994 estimate of $823,727,000. Funding for the Extramural Programs over the last 5 years has been as follows:

	Amount
FY 1990	$667,867,000
FY 1991	718,513,000
FY 1992	772,500,000
FY 1993	788,861,000
FY 1994	823,727,000

With the FY 1995 extramural request these funds will provide support for the following activities: Cellular and Molecular Basis of Disease Program, $253,541,000, an increase of $8,820,000 or 3.6% over the FY 1994 estimate of $244,721,000, Genetics Program, $241,598,000, an increase of $8,762,000 or 3.8% over the FY 1994 estimate of $232,836,000, Pharmacology and Biorelated Chemistry Program, $130,649,000, an increase of $3,975,000 or 3.1% over the FY 1994 estimate of $126,674,000, Biophysics and Physiological Science Program, $171,701,000, an increase of $5,354,000 or 3.2% over the FY 1994 estimate of $166,347,000, and Minority Opportunities in Research Program, $36,525,000, an increase of $1,740,000 or 5% over the FY 1994 estimate of $34,795,000.

CELLULAR AND MOLECULAR BASIS OF DISEASE PROGRAM BRANCH

The Cellular and Molecular Basis of Disease Program Branch supports research on the structure and function of cells, the hundreds of interacting molecules that make up cells and their changing environments, chemical and electrical signals that pass between and within cells, and cell growth and development. Understanding the characteristics of normal and abnormal cell activities provides the foundation for new strategies to prevent, treat, and cure diseases.

Among the most exciting research areas funded by the Cellular and Molecular Basis of Disease Program Branch are the following:

Biochemical Link Between Growth Factors and Cell Division: Researchers are now close to understanding the biochemical pathway by which the cells of higher organisms respond to external growth signals. First, molecules known as growth factors "dock" in specific receptors on the cell membrane. This triggers a series of biochemical reactions, culminating in the activation of molecules within the cell's nucleus, called transcription factors, that actually give the signal to turn on gene expression. Understanding this pathway, which until recently had baffled researchers, is critical to learning what causes cells to begin--and stop--dividing in embryonic and adult tissues. Thus, it has important implications for the understanding of diseases like cancer, in which cell division is out of control.

Studies by Drs. Alan Wolfman of the Cleveland Clinic Foundation and Michael Weber of the University of Virginia have identified a very significant biochemical mechanism that links the growth factor receptors and an oncogene (a gene implicated in the cause of cancer) called ras. The ras gene plays a critical role in the normal functioning of the pathway but is abnormally activated in some types of cancer, including colon cancer. Identification of the key molecules in this cell-signaling pathway should aid researchers seeking ways to control abnormal ras activation, as well as a wide array of other important cellular responses to signals for growth and differentiation.

Finding a Critical Streptococcus Gene: Streptococcus pyogenes (Group A) is a bacterium that causes serious infections, including rheumatic fever, scarlet fever, and the fatal toxic shock syndrome that caused the death of Jim Henson, creator of the Muppets. This bacterium is not efficiently eliminated by the body because an enzyme in its outer shell, hyaluronan (HA) synthase, is also a component of the human body. This makes it difficult for the immune system to recognize the bacterium as a foreign entity. Now, Dr. Paul Weigel of the University of Texas at Galveston has, for the first time, cloned and sequenced (determined the order of chemical bases in) the HA synthase gene of Streptococcus pyogenes. He has also purified the enzyme that this gene encodes. Despite years of effort by many investigators, until now none of the enzymes involved in the synthesis of the family of molecules that includes HA synthase had been purified. For this reason, Dr. Weigel's work is of enormous interest, both clinically and at the basic biochemical level. Knowledge of HA's three-dimensional structure may permit the development of drugs that would interfere with the serious infections this bacterium causes.

Tumor Suppressor Gene Characterized: Dr. Sumiko Inouye and colleagues at the University of Medicine and Dentistry of New Jersey have obtained critical information about a gene linked to tumor suppression in humans. Working with a bacterium called M. xanthus, the researchers isolated and sequenced the gene that codes for an enzyme called NDPK, which is essential for the bacterium's growth. The scientists have also obtained preliminary structural data on crystals of the enzyme.

This enzyme is one of the most highly conserved proteins known--an indication that it is critical to life in many organisms, from bacteria to humans. The human version of the enzyme, which is identical to the product of an oncogene, functions as a tumor suppressor by modifying proteins to inhibit tumor cell movement and metastasis. In fact, the oncogene product is being used as an indicator of how quickly breast cancer may spread. The information obtained by Dr. Inouye should be of considerable importance for understanding how NDPK functions in cell signaling, development, and metastasis.

Improved Understanding of a Molecule of the Year: Science magazine chose nitric oxide (NO) as its 1992 "molecule of the year" in recognition of NO's role in a wide variety of physiological functions. It has only recently been learned that NO is an important controller of blood pressure, penile erection, immune system responses, and nervous system functions. Given its importance, researchers are working hard to understand the chemical mechanisms by which this molecule produces its effects. In 1993, Dr. Baldomero M. Olivera of the University of Utah discovered one pathway by which NO mediates nerve cell responses. By studying reactions in the nerve tissues of the electric organ of the electric ray Torpedo californica, Dr. Olivera determined how the pathway functions in this model organism. Because NO is essential to so many activities, knowledge of the biochemical steps by which it produces its effects will aid in the design of drugs to treat many disorders.

Target for Reversing Antibiotic Resistance: The antibiotic vancomycin has been used for 25 years to treat infections caused by bacteria that are resistant to penicillin-type drugs or in patients who are allergic to these drugs. Very recently, however, some strains of bacteria have emerged that are also resistant to vancomycin. This is of particular concern in long-term care facilities and burn centers, where a penicillin-resistant form of Staphylococcus is often found. Extensive study of the chemical reaction by which vancomycin binds to, and weakens, the bacterial cell wall has revealed an explanation for resistance to the drug in some strains of bacteria. Dr. Christopher Walsh and coworkers at Harvard Medical School have found that a simple switch in types of chemical bonds probably lies at the heart of vancomycin resistance. The researchers have also identified a bacterial enzyme that may be a good target for a drug that could reverse the resistance.

GENETICS PROGRAM BRANCH

Research supported by the Genetics Program Branch has yielded new understanding of the structure of genes, how they work, and what they do. Almost daily, a newspaper article describes a medical, technological, or agricultural advance that is grounded in basic research on genetics. The biotechnology industry; gene therapy for the correction of genetic defects; and new strategies for diagnosing, treating, and curing diseases are among the most dramatic applications of genetics.

The following are examples of the research funded by the Genetics Program Branch.

DNA Repeat Expansions in Human Genetic Diseases: In the past few years, scientists have discovered that the genes associated with a number of well-known genetic conditions--Huntington's disease, myotonic dystrophy, fragile X syndrome, and others--as well as a gene associated with one form of colon cancer have a common defect. They all have long, unstable, repetitive regions of DNA.

Repetitive regions may consist of a single base, two bases, or as many as six bases lined up in tandem a number of times. These regions do not automatically cause disease; in fact, they are regularly found in normal genes. But in people who have certain diseases, these regions are abnormally long, involving, in extreme cases, as many as hundreds or thousands of copies of the repeated base(s). Evidence has been accumulating that the most severe forms of the diseases and the earliest disease onsets are associated with the longest repeats. Repeat expansions also account for the finding that many of these diseases become more severe in each succeeding generation of a family.

The first step toward controlling or repairing DNA repeat expansions is to determine how they arise. Drs. R. Michael Liskay of the Oregon Health Sciences University and Tom Petes of the University of North Carolina, Chapel Hill have identified two likely contributing factors--abnormal slippage of an enzyme that assists in the duplication of DNA and problems with genes that normally repair duplication errors. In repetitive regions, the zipperlike strands of DNA seem to zip up improperly, the enzyme slips and duplicates regions of the DNA repeatedly, and the errors that this creates go uncorrected.

These studies were carried out in yeast cells. Their relevance to human DNA duplication and repair is supported by the fact that human cells and yeast cells have many comparable structures and activities, including similar DNA repair genes.

Clues to the Onset of Emphysema: Emphysema is a major cause of disability in the United States. Breathing becomes extremely difficult, because the normal architecture of the lungs is dramatically altered. As in other tissues, cells in the lung are surrounded by a complex matrix of large molecules that are constantly degraded and replenished. The prevailing theory is that emphysema develops when there is an imbalance in the synthesis and degradation of these materials.

One matrix-degrading enzyme that has now been implicated in emphysema is collagenase. Dr. Kiran Chada of the University of Medicine and Dentistry of New Jersey developed a "transgenic" mouse model system in which mice produce excess human collagenase in their lungs. He showed that these mice develop a disease closely resembling emphysema. The walls of their lungs thin out and exhibit other structural changes that resemble those seen in the lungs of patients with emphysema. In general, the more collagenase present, the worse the animals' condition.

Dr. Chada's studies are the first to implicate collagenase directly in the development of emphysema. The mouse model system can now be used to test new treatments or other interventions for emphysema.

Dr. Chada has been successful in the past in developing transgenic mice that serve as models for other human diseases, specifically premature ovarian failure and non-growth hormone-deficient dwarf syndrome.

First 3-D Picture of a Transcription Complex: A picture is worth a thousand words--or more. Three-dimensional pictures are especially valuable because they show how the parts of a multi-component structure fit together, and they typically provide clues to how the parts interact, thereby linking the structure of a complex to its functions.

Dr. Steven Hahn of the Fred Hutchison Cancer Research Center in Seattle, Dr. Paul Sigler of Yale University, and their coworkers have produced the first three-dimensional picture of part of a transcription complex. Transcription complexes are the molecular machinery that turns gene expression on and off at exactly the right time and in the right cells throughout life; they are active in every cell in all living organisms--plants, animals, yeast, humans.

The images show that during the first step in the formation of the transcription complex, a saddle-shaped transcription protein straddles the DNA of the gene, which molds itself into a shape resembling the back of a horse. This protein plays a key role in initiating the transcription process innuclear genes of all types. By showing how DNA's shape changes when it is bound to the transcription protein, this work provides vital clues to the mechanics of gene regulation.

Human Immunity: Clues from Flies: When bacteria enter human cells, they trigger a series of events that result in an immune response that ultimately destroys the invading bacteria. The same is true when bacteria infect the cells of fruit flies.

In mammalian cells, bacterial invasion is associated with activation of a gene called NF-kB; the actions of this gene are closely tied to a variety of immune responses. Dr. Michael S. Levine of the University of California, San Diego has identified a counterpart of this gene in fruit flies, called Dif. Dif and NF-kB have structural similarities, and they encode similar proteins. In addition, they induce the production of similar bacteria-killing agents.

Dr. Levine and his colleagues have shown that, when the Dif protein accumulates in the nuclei of cells, it activates specific genes that produce proteins that can kill bacteria. The proteins exact their deadly toll by binding to and damaging the protective surface of the bacteria.

The close correspondence of the fruit fly and mammalian genes, gene products, and targets was unexpected and is a boon to researchers. Dif and NF-kB probably evolved from a common ancestral gene that was associated with immunity in a primitive organism. Scientists can now use the well-understood and genetically manipulatable fruit fly system for gaining insight into mammalian immune mechanisms.

PHARMACOLOGY AND BIORELATED CHEMISTRY PROGRAM BRANCH

In 1993, the name of the Pharmacological Sciences Program was changed to the Pharmacology and Biorelated Chemistry Program Branch. The new name more appropriately describes the research and training supported by the branch, and gives greater visibility to the branch's support of research in the chemical sciences. This support, along with that from other NIGMS branches, constitutes over 50 percent of the total NIH funding in this field.

The branch funds research ranging from basic chemistry, including the synthesis of chemicals and natural products with biological effects, to clinical investigations in such areas as the influences of genetics and metabolism on drug action. Insights into the structure, activity, and biological and molecular phenomena associated with key chemicals and drugs should enable researchers to design and develop new drugs and chemical tools. The following are examples of the work supported by the Pharmacology and Biorelated Chemistry Program Branch.

Immune Cells May Be "Engineered" for Gene Therapy: Dr. Stuart Schreiber and colleagues at Harvard University have inserted genes into immune system cells and used external regulators to turn the expression of these genes on and off. The regulators are chemicals patterned on drugs that suppress the immune system. Dr. Schreiber is an international leader in the chemical synthesis of immunosuppressants.

This work, though still far from clinical or other practical use, illustrates the pathway that basic research discoveries can follow. Although Dr. Schreiber's experiments were originally directed at understanding the chemical steps in immune responses and immune suppression, they may someday spin off products that will be of use in human gene therapy.

Cancer Clues from Drug Metabolism Variation: Many years of research on individual differences in drug metabolism have led to studies that suggest a connection between aggressive bladder cancer and the enzymes that metabolize the drug debrisoquine. Dr. Robert A. Branch of the University of Pittsburgh has been studying the possible relationships between levels of drug-metabolizing enzymes called cytochrome P-450's and the occurrence of certain types of cancer. He has obtained preliminary evidence suggesting that patients with bladder cancer have high levels of one type of P-450 enzyme. This type of enzyme is also associated with rapid metabolism of the drug debrisoquine. The study could indicate that these enzymes may also activate potential carcinogens once they enter the body. If true, a test for these enzymes could be developed to identify individuals who are at particular risk from certain environmental agents known to cause cancer.

Carbohydrate-Based Drugs May Block Inflammation: Recent discoveries that carbohydrates play important roles in many biological processes, including wound healing and inflammation, have dramatically increased researchers' interest in these molecules. Carbohydrates on the surfaces of cells can interact with invading microorganisms, adjacent cells, various proteins, and other substances. These interactions are now forming the basis for the design of drugs for many conditions, including arthritis and psoriasis. For example, binding interactions between proteins that cause the sticking of one cell to another (a process called cellular adhesion) and the proteins of skin cells are necessary to secure white blood cells to the skin surface--an important step in the inflammatory process necessary to wound healing. These interactions involve a carbohydrate called sialyl Lewis^x. Dr. Laura L. Kiessling of the University of Wisconsin has developed versatile new methods for the synthesis of important carbohydrates and is preparing variants of sialyl Lewis^x that may inhibit, rather than promote, cell adhesion. These compounds could be used to reverse inflammation in disorders such as rheumatoid arthritis, multiple sclerosis, and toxic shock. Dr. Kiessling's work builds on that of long-term NIGMS grantee Dr. Kyriacos Nicolaou of the Scripps Research Institute, who recently accomplished the first chemical synthesis of sialyl Lewis^x. This advance should speed research on sialyl Lewis^x, because without chemical synthesis, the carbohydrate is extremely expensive and difficult to obtain.

Anesthesia May Be Safe for Patients with Respiratory Infections: Every year, thousands of surgeries are canceled or postponed due to viral infections. As a result, costs to patients and the health care system are greatly increased. Now, research by Dr. Paul Knight of the State University of New York at Buffalo and Dr. Alan Tait of the University of Michigan indicates that anesthesia may not worsen the outcome for surgical patients with upper respiratory tract infections, as previously believed. In fact, in the pediatric patients the researchers studied, postsurgical illness was actually reduced. The scientists followed this observation with laboratory studies that demonstrated that anesthetics block the proliferation of viruses. In addition to possibly preventing the postponement of scheduled surgery, this discovery of the effects of anesthetics on viruses could have implications for the treatment of patients with viral infections, including AIDS.

Healing Poisons: Drs. Maureen Bonness and Tom Mabry of the University of Texas at Austin have found a group of toxins that they call RIP's (for ribosome-inactivating proteins) that may have uses as "magic bullets" for selectively killing cancer cells or infectious agents. RIP's, which are present in the cells of a broad range of plants--including corn, carnations, and mistletoe--disrupt cell organelles called ribosomes. This, in turn, blocks the production of proteins. In a cancer cell, such an attack on a ribosome might effectively stop the runaway production of new cancer cells. The scientists are now exploring techniques for delivering RIP's to target cells.

BIOPHYSICS AND PHYSIOLOGICAL SCIENCES PROGRAM BRANCH

Nowhere is the exquisite order of nature more striking than in the arrangement of atoms within the proteins and nucleic acids that make up the human body. The study and determination of the structures of these molecules and their importance in human health are at the heart of the Biophysics and Physiological Sciences (BPS) Program Branch. An area of special emphasis in the branch is the application of the information derived from an understanding of the role of selected molecules in the healing of burns and other forms of trauma.

The following are examples of the research areas funded by the BPS Program Branch.

New Lead in Lou Gehrig's Disease: Sometimes an observation links research activities in previously separate fields. In early 1993, scientists announced that they had identified the gene that is defective in the hereditary form of amyotrophic lateral sclerosis. Surprisingly, the gene turned out to encode superoxide dismutase (SOD), an enzyme that has been studied for years by NIGMS grantees. Because SOD had been well characterized, scientists were in an ideal position to move quickly once the connection to ALS was made.

The association of the SOD enzyme with ALS immediately suggests that people with the disease might benefit from properly working SOD molecules or drugs that mimic SOD activity. Researchers are optimistic that therapies based on restoring SOD activity will help people with both the hereditary and nonhereditary forms of the disease, since the signs and symptoms of disease in the two forms of ALS are indistinguishable.

Structural studies by Drs. John Tainer and Elizabeth Getzoff of the Scripps Research Institute in La Jolla, California, showed that, in individuals with the hereditary form of the disease, the detailed structure of the SOD enzyme is different. Changes in a few key amino acid building blocks in SOD cause these changes in the folded structure of the protein. As a result of the structural changes, ALS SOD cannot carry out its normal function--the conversion of a highly reactive, deadly form of oxygen to theform of oxygen we breathe. Exactly why nerve cells and not other cells (all of which contain SOD) are so severely affected by this change in SOD structure remains a mystery.

Dr. Joan Valentine of the University of California, Los Angeles, who has studied mutant SOD molecules for some time, is now examining the specific mutants implicated in ALS to better understand exactly why they fail to remove the deadly form of oxygen.

Biological Molecules Offer Promise for Higher Technology: Nanotechnology, which combines extreme miniaturization (at the level of a billionth of a meter) and molecular structures, is the technology of the future. The tiny components of nanodevices are not gears or wheels or chips; they are molecular machines composed of precisely placed atoms that derive inspiration from proteins, nucleic acids, and other biological molecules. The speed and capacity of these devices will exceed by hundreds, millions, or billions of orders of magnitude the speed and capacity of available electronic devices, while their size will be diminished to a similar extent. The supercomputer in a nanotechnological world, for example, might hold data on a single atom that today are stored on a billion atoms. Similarly, the vast amount of data that today can be stored on a single CD could be stored in a nanomachine the size of a cell's nucleus.

Nanotechnology is a spinoff of NIGMS-supported fundamental biophysical studies of the structure and properties of atoms and molecules. Nanodevices will require "scaffolding" materials, and studies by Dr. Nadrian Seeman of New York University show that DNA molecules could fill this function. Like Tinkertoy® sticks, DNA can be assembled in a variety of configurations and then draped with informational molecules. Bacteriorhodopsin, a protein that converts light into energy, is likely to be one such information-storing molecule. Dr. Robert Birge of Syracuse University is developing three-dimensional "biochips" of bacteriorhodopsin to carry out memory and computing activities that are done today by silicon chips.

Controlling Traffic Through Cell Membrane Channels: Potassium, sodium, chloride, and other essential ions (charged molecules) enter and leave cells through porelike channels in cell membranes. Channels have "gates" that open and close in response to chemical or electrical signals. Several diseases, including cystic fibrosis and epilepsy, are associated with ion channels that have faulty gates.

Dr. Isabella A. Karle of the U.S. Naval Research Laboratory in Washington, DC, the 1993 recipient of the prestigious Bower Award and Prize in Science, has located the latch that controls the opening of the gate on a potassium ion channel in the membranes of soil spores. Through high-resolution structural studies of channel proteins, she has determined the position of every atom in the potassium channel protein. Dr. Karle's pictures show exactly how, when the gate is open, potassium ions can freely travel from atom to atom along the channel, and how, when a hydrogen bond forms between atoms on the opposite side of the channel, the gate is closed and ion passage is blocked. Scientists may learn from these studies how to open and close gates in channels and, in this way, correct problems in cells that have defective gates.

Molecules that Help to Heal Wounds: One key to the reduction of hospitalization costs is speeding up the healing of wounds. Wounds (including burns, surgical incisions, and ulcers) account for much illness and many deaths in this country and around the world. The leading cause of death for people under age 40 in the United States is trauma, and among the elderly, people with diabetes, and those who suffer spinal cord injuries, slow-healing ulcers are a major health problem. According to one estimate, some 4 million Americans have wounds that are failing to heal, at an annual health care cost exceeding $9 billion.

In November 1993, the BPS Program Branch sponsored a workshop on the molecular and structural biology of tissue repair. The meeting brought together clinicians who treat wounds, scientists who investigate the effects of cytokines on wound healing, and biophysicists who determine the detailed structures of cytokines. Cytokines are molecular growth factors that are released from cells at the site of a wound. They attract cells and other factors to the site to clot blood, clean up the wound, curb infection, and rebuild the damaged tissue and skin. To date, more than 20 cytokines have been identified, and the structures of most have been determined.

A striking feature of the structural studies is that several of the cytokines share common architectures. This observation, combined with structural studies of the interactions of these cytokines with their receptors on cell membranes, will greatly facilitate the design of modified cytokines. Clinicians of the future could use these compounds to enhance or block elements of the inflammatory process associated with wound repair.

In an important clinical study presented at the meeting, Dr. Thomas Mustoe of Northwestern University Medical School reported on the wound-healing properties of one cytokine, platelet-derived growth factor. This cytokine promotes the production of collagen, blood vessels, and skin cells. In preliminary studies in patients with bedsores and foot ulcers (a common problem for people with diabetes), platelet-derived growth factor showed promise for easing pain during tissue repair and for helping bedsores heal.

Closer Look at a Key AIDS Virus Protein: Finding a cure for AIDS has frustrated the research and medical communities for more than a decade. New strategies for the treatment of this disease may come from basic studies of the molecular interactions of components of the AIDS virus with components of host cells. The aim is to block the reproduction of the AIDS virus through the design of drugs to prevent key components of the virus from working.

An appealing target for the design of such drugs is the viral protein reverse transcriptase (RT). If RT's activities could be blocked completely, the infection would be stopped, because without RT, AIDS viruses cannot commandeer the host cell machinery to reproduce. Since host cells do not have RT-like enzymes, drugs that block RT are unlikely to be toxic to host cells or to affect their normal function.

In 1992, progress was reported on determining the atom-by-atom structure of RT. Building on that work, Drs. Edward Arnold of the Center for Advanced Biotechnology and Medicine at Rutgers University (supported by the National Institute of Allergy and Infectious Diseases) and Stephen Hughes of the Advanced BioScience Laboratories Basic Research Program in Frederick, Maryland, have recently published more extensive and higher-resolution data on the structure of RT bound to its target molecule. These additional details about this important interaction are an essential step in the design or identification of drugs that can more effectively block the actions of this key player in AIDS infection.

MINORITY OPPORTUNITIES IN RESEARCH PROGRAMS BRANCH

The Minority Opportunities in Research (MORE) Programs Branch is the focal point for the Institute's efforts to increase the number and capabilities of underrepresented minority individuals engaged in biomedical research. The goal of the branch is to encourage more minority students to pursue training for scientific careers and to enhance the science curricula and research capabilities of faculty at institutions with substantial minority enrollments.

The branch has three components: the Minority Access to Research Careers Program, the Minority Biomedical Research Support Program, and Special Initiatives. MORE's activities give NIGMS the lead role at NIH in research and research training activities targeted at underrepresented minorities.

Minority Biomedical Research Support Program: MBRS grants to minority institutions support research projects by faculty members and provide opportunities for students to work as part of a research team. This support has the added benefit of strengthening the institutions' biomedical research capabilities. Awards are also made to permit enrichment activities, such as attendance by faculty and students at scientific meetings and participation in research during the summer at off-campus laboratories. In FY 1993, 683 faculty members at 98 institutions worked on 589 MBRS research projects, and 937 undergraduate and 415 graduate students participated in these projects as research assistants.

The positive impact of the MBRS Program is illustrated by the success of these recent participants:

- Dr. Gabriel Barletta, a former graduate student in the MBRS Program at Rutgers University who was introduced to the MBRS Program at Bronx Community College in New York, continued his education and participation in research in the MBRS Program at the State University of New York at Old Westbury. He is now doing a postdoctoral fellowship in biochemistry at the Massachusetts Institute of Technology.

- Dr. Alice Garner, a former graduate student in the MBRS Program at Southern University in Baton Rouge, Louisiana, is now an assistant professor of clinical pediatrics at the University of Southern California School of Medicine, where her research focuses on the effects of bacteria on brain blood vessels.

- At Johnson C. Smith University, a small historically Black college in North Carolina, the MBRS Program has supported three faculty members and six to eight students per year. Since 1983, 11 of the MBRS students have completed the Ph.D. degree and another 20 have completed the M.S. degree.

Minority Access to Research Careers Program: The MARC Program provides special research training opportunities for students and faculty at educational institutions with substantial minority enrollments. The program enables grantee institutions to develop and strengthen their biomedical research training capabilities through improved science curricula, seminars, off-campus research experiences, and other special initiatives. As a result, these schools are able to graduate more students who go on to doctoral study and pursue biomedical research careers.

MARC accomplishes these goals through four support mechanisms: Honors Undergraduate Research Training Grants, Honors Predoctoral Fellowships, Faculty Fellowships, and the Visiting Scientist Program. In addition, the MARC Program provides conference support to organizations and institutions that are active in the recruitment and retention of minority scientists. In FY 1993, 559 students at 63 institutions participated in MARC's honors undergraduate program, 6 faculty members received training and/or degrees through the faculty fellowship program, and 73 students received MARC predoctoral fellowships.

Program highlights include:

- Dr. Mabel Duyao, a former MARC honors undergraduate student at the University of Hawaii at Manoa, is a member of the team of scientists at Massachusetts General Hospital that discovered the gene involved in Huntington's disease. Dr. Duyao earned both an M.A. and a Ph.D. in biochemistry from Boston University.

- Jose Meza, a MARC student at California State University, Long Beach, was selected as the school's Outstanding Graduate for 1993. After graduating in May 1993, he is now pursuing his Ph.D. in molecular and cellular biology at the University of California, Berkeley.

- Maria Rivera, a former MARC honors student at Catholic University of Puerto Rico in Ponce, recently was accepted into the NIGMS Pharmacology Research Associate Program. She will do postdoctoral research in the laboratory of Dr. Michael Boyd at the National Cancer Institute. Ms. Rivera is currently pursuing a Ph.D. in pharmacology/toxicology at the University of Texas at Austin as a MARC predoctoral fellow.

Special Initiatives: As a complement to the MARC and MBRS Programs, the MORE Programs Branch supports several special initiatives that strive to develop new approaches for the recruitment and retention of minority biomedical scientists. Individuals supported through these special initiatives range from high school students to faculty members. One such initiative is the national predoctoral fellowships for minorities. In FY 1993, the third year of this effort, NIGMS awarded 18 fellowships, bringing its total to 114. Other NIH components have joined the NIGMS effort, supporting an additional 120 fellows since the program's inception.

Another initiative, the Bridges to the Future Program, is administered by NIGMS in cooperation with the NIH Office of Research on Minority Health. These grants encourage students in associate degree or master's degree programs to make the transition to the next levels of training (the bachelor's degree and Ph.D. degree, respectively) in pursuit of careers in biomedical research. Now in its second year, the program has funded 40 awards, 31 of which were made in FY 1993.

Finally, the section is continuing to mount regional workshops to encourage participation by academic institutions that are not presently supported by either the MARC or MBRS Program. Workshops have been held in Charlotte, North Carolina; New Orleans, Louisiana; and Albuquerque, New Mexico.

INTRAMURAL RESEARCH PROGRAM

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Estimate		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
19	$1,180,000	19	$1,158,000	17	$1,105,000	-2	-$53,000

Rationale for the Budget Request

The FY 1995 budget estimate for the Intramural Research Program is $1,105,000, a decrease of $53,000 over the FY 1994 estimate. Funding for the Intramural Research Program during the last 5 years has been as follows:

	Amount	FTE
FY 1990	$1,072,000	20
FY 1991	1,082,000	18
FY 1992	1,136,000	19
FY 1993	1,180,000	19
FY 1994	1,158,000	19

NIGMS has a small, but unique, intramural research program, known as the Pharmacology Research Associate (PRAT) Program. Under its auspices, a group of recently trained scientists is selected each year for a 2-year period of postdoctoral research experience under the direction of preceptors in the intramural laboratories of the various categorical institutes of the National Institutes of Health. The goal of this program is to develop topflight leaders in pharmacological research who will take key positions in academic, industrial, and government research laboratories.

Profile of PRAT Program Participants: Since its establishment in 1965, 269 scientists have graduated from the PRAT Program. It is known that at least 245 (91 percent) of them have entered research careers. Among the PRAT graduates, 115 are located at academic or independent research institutions, 103 are at NIH or other Federal research facilities, and 38 are at pharmaceutical firms. Almost 42 percent of the PRAT graduates who are engaged in research possess an M.D. degree, indicating that the program has succeeded in attracting a large number of physicians and directing them into research careers instead of into clinical practice.

PRAT Graduate Proposes New Alzheimer's Theory: Former PRAT fellow (1977-78) Dr. Warren J. Strittmatter and his colleagues at Duke University have recently presented evidence in support of a new hypothesis for the underlying cause of late-onset Alzheimer's disease. Their theory is a radical departure from most current Alzheimer's research, which focuses on the role of a

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specific protein, beta-amyloid, in the degeneration of nerve cells. The researchers propose that two variants of a cholesterol-carrying protein, apolipoprotein E, provide protection against the development of Alzheimer's disease, and that people who do not inherit these variants lose some or all of that protection. While still very preliminary, this hypothesis offers exciting possibilities for therapy as well as diagnostic tests. Theoretically, if lack of a protective factor leads to Alzheimer's disease, treatment could be as simple as adding the factor.

RESEARCH MANAGEMENT AND SUPPORT

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Estimate		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
172	$25,344,000	169	$26,681,000	167	$27,159,000	-2	+$478,000

Rationale for the Budget Request

For FY 1995, the Research Management and Support budget request is $27,159,000, an increase of $478,000 over the FY 1994 estimate. Funding for the Research Management and Support budget during the last 5 years has been as follows:

	Amount	FTE
FY 1990	$22,317,000	153
FY 1991	22,626,000	166
FY 1992	24,970,000	173
FY 1993	25,344,000	172
FY 1994	26,681,000	169

The Research Management and Support budget provides funds for salaries, equipment, supplies, and other administrative expenditures that support the NIGMS extramural staff. Leading the Institute is the Office of the Director, which has traditionally provided the overall administrative guidance, direction, and oversight of the Institute's scientific program areas. By maintaining contact with the scientific and academic communities, the Office of the Director is perpetually conscious of the public's health and research concerns, which are reflected in the development and planning of the Institute's programs and policies. NIGMS continues to evaluate the research it supports and project future needs for new or expanded areas of investigation based on promising areas of biomedical research. A major portion of the funds in this budget is reserved for both the scientific review and administration of grants and contracts, as well as for the related fiscal stewardship function.

The Research Management and Support budget also funds: those services provided by central NIH components, such as the Division of Research Grants, program evaluation studies, and the National Advisory General Medical Sciences Council.

For FY 1995, the Research Management and Support budget request is $27,159,000 an increase of $478,000 above the FY 1994 estimate.

In FY 1995, the National Institute of General Medical Sciences will continue efforts to streamline its current management strategies and develop new administrative processes to achieve efficiency and maintain its overall effectiveness in support of its mission. The NIGMS program staff will provide the general oversight and direction for approximately 4,536 grants and 7 research and development contracts to be supported by the Institute in FY 1995. In addition, NIGMS management and scientific staff will continue to review the Institute's grant portfolios and maintain up-to-date knowledge of promising areas of biomedical research. Specifically, the staff's activities include ensuring rigorous scientific and financial administration of grant-supported programs; conducting peer review of competing training grant applications to determine their scientific and program merit; serving as knowledgeable contacts for applicants, grantees, advisory groups, and other organizational components of the Department of Health and Human Services, the Public Health Service, private associations, and other Federal Government agencies; and compiling and reporting the scientific and financial information pertinent to the Institute's various grant programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director.......	35	34	34
Office of Administrative Management.................	37	36	34
Office of Program Activities.	51	51	51
Biophysics and Physiological Sciences Program Branch.....	11	11	11
Pharmacology and Biorelated Chemistry Program Branch...	31	30	28
Cellular and Molecular Basis of Disease Program Branch...	10	10	10
Minority Opportunities in Research Programs Branch....	5	5	5
Genetics Program Branch......	11	11	11
Total, NIGMS............	191	188	184

Average GS/GM Grade

1990..................................	9.8
1991..................................	9.7
1992..................................	10.0
1993..................................	10.2
1994..................................	10.1
1995..................................	10.1

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FISCAL YEAR 1995

Volume V

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
National Institute of Child Health and Human Development
National Eye Institute
National Institute of Environmental Health Sciences
National Institute on Aging
National Institute on Deafness and Other Communication Disorders

Justification of
Estimates for
Appropriations Committees

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

	FY 1995 Estimate		Page
	FTEs	Amount	Number
National Institute of Child Health and Human Development...............	508	$516,736,000	1
National Eye Institute................	249	292,022,000	49
National Institute on Environmental Health Sciences.....................	715	267,955,000	85
National Institute on Aging...........	445	433,701,000	123
National Institute of Arthritis and Musculoskeletal and Skin Diseases...	150	228,413,000	161
National Institute on Deafness and Other Communication Disorders.......	117	168,689,000	201

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

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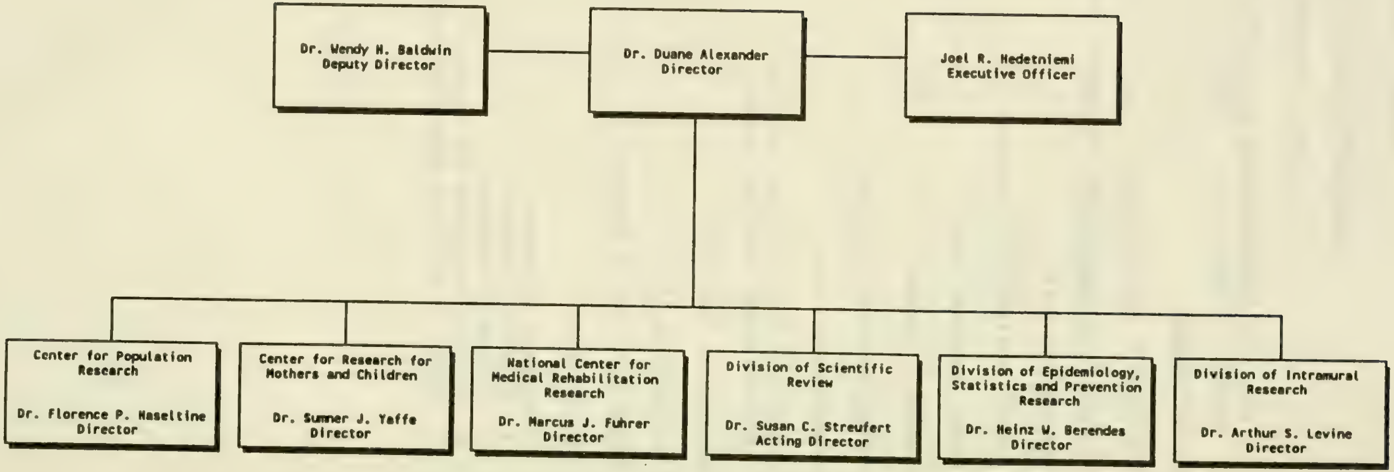
NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Organization Structure


Dr. Wendy H. Baldwin
Deputy Director
Dr. Duane Alexander
Director
Joel R. Hedetniemi
Executive Officer
Center for Population Research
Dr. Florence P. Haseltine
Director
Center for Research for Mothers and Children
Dr. Sumner J. Yaffe
Director
National Center for Medical Rehabilitation Research
Dr. Marcus J. Fuhrer
Director
Division of Scientific Review
Dr. Susan C. Streufert
Acting Director
Division of Epidemiology, Statistics and Prevention Research
Dr. Heinz W. Berendes
Director
Division of Intramural Research
Dr. Arthur S. Levine
Director

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to child health and human development, [$555,195,000] *$516,736,000 of which $6,081,000 shall not become available for obligation until September 19, 1995.* (Department of Labor, Health and Human Services, and Education, and Related Agencies Appropriation Act, 1994.)

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National Institute of Child Health and Human Development

Language Analysis

Language Provision	Explanation
"...of which $6,081,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation..................	$534,094,000	$555,195,000	$516,736,000
Section 511 8% reduction.......	-4,273,000	---	---
Section 513 consultant services reduction..................	-29,000	---	---
Section 216 S&E reduction......	-2,004,000	---	---
Subtotal, adjusted appropriation.............	527,788,000	555,195,000	516,736,000
Real transer to other NIH accounts for tuberculosis research..	-21,000	---	---
Comparative transfer to the Office of AIDS Research, NIH for HIV activities.........	-38,807,000	-56,426,000	---
Subtotal, adjusted budget authority.................	488,960,000	498,769,000	516,736,000
Unobligated balance lapsing....	---	---	---
Total obligations...........	488,960,000	498,769,000	516,736,000

1/ Excludes the following amouts for reimbursable activities carried out under this account: 1993 -- $22,416,000 and 4 FTEs; 1994 -- $20,496,000 and 3 FTEs; 1995 -- $20,496,000 and 3 FTEs.

Note: Excludes $92,780 for royalties received in FY 1993 and $92,780 in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Mechanism

	1993 Actual		1994 Current Estimate		1995 Estimate	
Research grants:	No.	Amount	No.	Amount	No.	Amount
Research projects:						
Noncompeting..................	987	$200,292,000	960	$202,512,000	927	$204,657,000
Admin. supplementals..........	(93)	3,903,000	(80)	3,750,000	(80)	3,900,000
Competing:						
Renewal.......................	153	37,225,000	138	34,043,000	140	36,246,000
New...........................	210	29,346,000	189	26,798,000	192	28,604,000
Supplemental..................	3	194,000	3	197,000	3	205,000
Subtotal, competing.......	366	66,765,000	330	61,038,000	335	65,055,000
Subtotal, res. proj.......	1,353	270,960,000	1,290	267,300,000	1,262	273,612,000
Research centers:						
Specialized/comp. centers.....	75	48,082,000	77	50,023,000	78	52,774,000
Other research:						
Research career program.......	78	7,309,000	78	7,485,000	79	7,775,000
Coop. clin. research..........	41	21,248,000	39	20,924,000	44	23,561,000
BRS...........................	--	---	--	---	--	---
Minor. biomed. res. support...	--	513,000	--	569,000	--	585,000
Other research related........	36	3,040,000	37	3,138,000	37	3,226,000
Subtotal, other research....	155	32,110,000	154	32,116,000	160	35,147,000
Total, research grants..........	1,583	351,152,000	1,521	349,439,000	1,500	361,533,000

Training						
Individual awards:						
Noncompeting	56	1,901,000	64	1,981,000	69	2,195,000
Competing	59	1,548,000	28	881,000	23	748,000
Subtotal, individ	115	3,449,000	92	2,862,000	92	2,943,000
Institutional awards:						
Noncompeting	543	11,360,000	523	11,434,000	507	11,395,000
Competing	108	2,473,000	135	3,465,000	151	3,921,000
Subtotal, inst	651	13,833,000	658	14,899,000	658	15,316,000
Total, training	766	17,282,000	750	17,761,000	750	18,259,000
Research and development contracts	77	25,684,000	79	33,131,000	79	37,542,000
	FTEs		FTEs		FTEs	
Intramural research	363	69,628,000	334	73,074,000	319	73,004,000
Research management and support	199	25,214,000	189	25,364,000	189	26,398,000
Total	562	488,960,000	523	498,769,000	508	516,736,000
Clinical Trials		(47,054,000)		(48,800,000)		(54,600,000)

Note--Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Summary of Changes

1994 Estimated budget authority	$498,769,000
1995 Estimated budget authority	516,736,000
Net Change	+17,967,000

	1994 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$25,957,000		+$311,000
b. One less day of pay		25,957,000		-101,000
c. Annualization of January 1994 locality pay increase		25,957,000		+235,000
d. January 1995 pay increases		25,957,000		+317,000
e. Federal employees compensation fund, unemployment compensation		124,000		+12,000
f. Federal telecommunications system		65,000		+5,000
g. Payment for centrally furnished services		20,606,000		+847,000
h. Service and supply fund increase		5,700,000		+258,000
i. Increased costs for services and supplies		20,811,000		+600,000
Subtotal				2,484,000
2. Research Management and Support				
a. Within grade increase		$11,847,000		+141,000
b. One less day of pay		11,847,000		-46,000
c. Annualization of January 1994 locality pay increase		11,847,000		+107,000
d. January 1995 pay increases		11,847,000		+145,000
e. Federal employees compensation fund, unemployment compensation		124,000		+5,000
f. Federal telecommunications system		65,000		+3,000
g. Payment for centrally furnished services		6,348,000		+261,000
h. Service and supply fund increase		1,900,000		+65,000
i. Increased costs for services and supplies		5,269,000		+860,000
j. DHHS Working Capital Fund		499,000		+4,000
Subtotal				+1,545,000

Summary of Changes--continued

	1994 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
B. Program:				
1. Research project grants:	No.	Amount	No.	Amount
a. Noncompeting...........	960	206,262,000	-33	+2,295,000
b. Competing..............	330	61,038,000	+5	+4,017,000
Total..................	1,290	267,300,000	-28	+6,312,000
2. Research centers............	77	50,023,000	+1	+2,751,000
3. Other research..............	154	32,116,000	+6	+3,031,000
4. Research training...........	750	17,761,000	---	+498,000
5. Research and development contracts.................	79	33,131,000	---	+4,411,000
	FTE		FTE	
6. Intramural research.........	334	73,074,000	-15	-2,554,000
7. Research management and support...................	189	25,364,000	---	-511,000
Subtotal................				+13,938,000
Total changes...................				+17,967,000

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NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	523	508	-15
Full-time equivalent of overtime and holiday hours.................	5	5	---
Average ES salary.....................	$109,800	$111,500	+$1,700
Average GM/GS grade....................	10.4	10.4	---
Average GM/GS salary...................	$48,000	$49,400	+$1,400
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).....................	$78,300	$80,300	+$2,000
Average salary of ungraded positions..	$24,000	$24,800	+$800
Personnel compensation:			
Full-time permanent.................	$17,551,000	$17,488,000	-$63,000
Other than full-time permanent......	7,484,000	7,451,000	-33,000
Other personnel compensation........	1,333,000	1,331,000	-2,000
Special personnel service payments..	5,002,000	4,981,000	-21,000
Total personnel compensation.....	31,370,000	31,251,000	-119,000
Personnel benefits.....................	6,415,000	6,390,000	-25,000
Benefits for former personnel..........	19,000	20,000	+1,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Travel and transportation of persons...	1,135,000	1,180,000	+$45,000
Transportation of things...............	160,000	160,000	---
Rental payment to GSA..................	---	14,000	+14,000
Rental payment to others...............	497,000	497,000	---
Communications, utilities, and misc....	1,318,000	1,313,000	-5,000
Printing and reproduction..............	470,000	470,000	---
Other services:			
Consulting services.................	721,000	745,000	+24,000
Other Services......................	7,331,000	7,349,000	+18,000
Purchases from Gov't Accoounts......	39,567,000	40,491,000	+924,000
R&D Contracts.......................	28,231,000	32,542,000	+4,311,000
Supplies and materials.................	7,535,000	7,535,000	---
Equipment..............................	6,800,000	6,987,000	+187,000
Grants, subsidies, & contributions.....	367,200,000	379,792,000	+12,592,000
Total budget authority.............	498,769,000	516,736,000	+17,967,000

Note: Includes FTEs associated with HIV Reearch Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NICHD

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	17,551	17,551	17,488	(63)
11.3	Other than full-time permanent	7,484	7,484	7,451	(33)
11.5	Other personnel compensation	1,333	1,333	1,331	(2)
11.8	Special personnel services payments	5,002	5,002	4,981	(21)
11.9	Subtotal, personnel compensation	31,370	31,370	31,251	(119)
12.1	Civilian personnel benefits	6,415	6,415	6,390	(25)
13.0	Benefits for former personnel	19	19	20	1
	Subtotal Pay Costs	37,804	37,804	37,661	(143)
21.0	Travel and transportation of persons	1,235	1,135	1,180	45
22.0	Transportation of things	160	160	160	0
23.2	Rental payments to others	497	497	497	0
23.3	Communications, utilities, and miscellaneous charges	1,318	1,318	1,313	(5)
24.0	Printing and reproduction	470	470	470	0
25.0	Other Services	42,619	40,160	41,026	866
26.0	Supplies and materials	7,535	7,535	7,535	0
	Subtotal non-pay costs	53,834	51,275	52,181	906
	Total Administrative Costs	91,638	89,079	89,842	763

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1994 House Report	
Vaccines	
1. The House in its report 103-156, page 61 stated..."The Committee encourages the Institute to continue work to develop and test vaccines, including completion of clinical trials on the pertussis vaccine, and to conduct trials of vaccines that offer immunity to intestinal infections."	1. Vaccines are one of the most important and efficient means of preventing some of the most serious childhood infections. The NICHD is currently testing the efficacy of a new acellular pertussis vaccine in an infant population in Sweden. Results of the Swedish studies should be available in October 1994. The adverse side effects of this vaccine have been negligible so far. A U.S. trial of this vaccine for safety and immunogenicity began in Fall 1993. This trial is scheduled for completion in late 1994. NICHD researchers are currently using the novel conjugate technology to develop vaccines for bacillary dysentery, Shigellosis, cholera, and hospital-acquired bacteremia. Clinical trials are under discussion to test the effectiveness of a new typhoid vaccine for infants and children under age 2. A trial has recently begun to test a Group B strep/tetanus toxoid conjugate vaccine to prevent newborn Group B strep sepsis. Intramural researchers also are attempting to use the capsular polysaccharides of Mycobacterium tuberculosis to produce a new conjugate vaccine for pulmonary tuberculosis, a disease that is

Item	Action Taken or to be Taken
	fast becoming the nation's newest public health threat.
Rett Syndrome	
2. The House in its report 103-156, page 61 stated..."Rett's syndrome is a progressive neurological disorder that affects only females which results in profound mental and physical retardation. Within the increase provided for NICHD, the Committee believes that expansion of research into this disorder should be a high priority."	2. The NICHD provides the major support for research on Rett syndrome. NICHD is currently supporting two large program projects made up of eleven subprojects that are studying various aspects of this disorder, including its clinical manifestations, neurophysiology, neuropathology, molecular genetics, neurochemistry, biochemistry, and neuroimaging. In addition, program staff is working with several investigators to develop research applications that could lead to a better understanding of this disorder.
Center for Medical Rehabilitation Research (NCMRR)	
3. The House in its report 103-156, page 61 stated..."The Committee intends that additional resources above the request be allocated to the NCMRR to enhance its research initiatives."	3. The NICHD is pleased with the progress of the new National Center for Medical Rehabilitation Research. The FY 1994 Appropriation for the Center is $14,000,000 in extramural funding. This compares to $10,643,000 in the FY 1994 Request and $9,995,000 in FY 1993 obligations.
Sudden Infant Death Syndrome	
4. The House in its report 103-156, pages 61/62 stated..."The Committee urges the NICHD to maintain its ongoing SIDS research efforts and to implement new programs for the fifth year of the SIDS five-year research plan."	4. The NICHD five-year research plan is directed toward acquiring knowledge to identify infants at risk for SIDS and to prevent SIDS deaths. In FY 1994 NICHD will continue with studies on the association of infant sleep position and SIDS infant

Item	Action Taken or to be Taken
	physiology under different sleep conditions, the contribution of environmental factors like bedding and heating to SIDS, and a multicenter clinical trial of apnea monitors. The Institute is also planning studies to understand how the brain abnormalities observed in SIDS infants originate, and to develop methods to detect the abnormalities in infants before death.
Childhood Development 5. The House in its report 103-156, page 62 stated..."The Committee understands that the Institute has begun developing a request for applications and will provide funding for research on middle childhood development in fiscal year 1994. The Committee commends NICHD for responding to this critical area of research, and urges the Institute to continue supporting research in this area."	5. The NICHD is continuing its long term research initiative on development during middle childhood. The NICHD is co-sponsoring a Request for Applications with the NIMH and plans to support six to eight scientifically meritorious applications on this topic. The research to be conducted should reveal social, emotional and cognitive patterns related to normal development in this crucial part of the life span. In addition, some of the new knowledge obtained should provide clues about factors that lead to development of health risk behaviors that have the potential for leading children awry as they enter their adolescent years.
Normative Behavior 6. The House in its report 103-156, page 62 stated..."The Committee believes this program should remain a priority at the Institute and urges NICHD to continue funding in fiscal year 1994 for this important area of research."	6. Minority children constitute a rapidly growing segment of the population, and the scientific documentation of their normative development and conditions that influence it are important and need to be investigated. In January 1993, the NICHD awarded grants to five investigators who responded to a Request for Applications about the normative

Item	Action Taken or to be Taken
	behavioral development of ethnic minorities. The NICHD also funds research on the development of minority children through its investigator initiated research program and through the support of the NICHD Study of Early Child Care that follows the development of 253 minority children from birth through age seven.
Bionutrition	
7. The House in its report 103-156, page 62 stated..."The Committee is encouraged by the work which has been done in the bionutrition area by NICHD, particularly its work related to low birth-weight children and improving the outcomes of pregnancies among minority women utilizing nutritional interventions. The Committee has provided funding for NICHD to increase its efforts in the area of bionutrition."	7. The NICHD supports bionutrition research designed to increase understanding of nutrient function at the cellular and molecular levels. Bionutrition research also addresses the effects of excesses, deficiencies, and interactions of nutrients on fetal development, cell differentiation, brain function, drug metabolism, and hormone synthesis. On the basis of recent findings indicating a strong relationship between low maternal zinc levels and decreased fetal growth, the NICHD is currently funding a randomized clinical trial of zinc supplementation in pregnancy in 600 black women. Its goal is to reduce preterm birth, growth retardation and perinatal infection. The NICHD is also currently funding a clinical trial to determine the effects of oral calcium supplementation on bone density in adolescent girls. Findings from this study imply that calcium supplementation during adolescence can increase peak bone density and may protect young women against

Item	Action Taken or to be Taken
	future osteoporosis and bone fractures.
Infertility	
8. The House in its report 103-156, page 62 stated..."The Committee remains supportive of this research and would particularly urge the Institute to expand its activities in the area of male infertility."	8. Up to 40 percent of infertility in the human is associated with male factors. Male infertility is currently not well understood. In addition to the poorly understood qualitative factors whose abnormalities contribute to male infertility, recent reports of a widespread decline in sperm counts have raised the question of whether this phenomenon has contributed to male infertility. As very few couples with a female of normal fertility ever have a readily identifiable or treatable problem such as male hypogonadism, the empirical use of costly assisted reproductive technologies, including hormonal enhancement treatment of the female, has been widely practiced. The current status of treating male fertility problems is discouraging with some reports indicating only a 20 percent success rate in fathering a child over a 2 year treatment plan. The NICHD recently held a workshop on male spermatogenesis and is developing an initiative on idiopathic (unexplained) male infertility designed to accelerate research in this important area of reproductive health care.

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Item	Action Taken or to be Taken
1994 Senate Report	
Normative Behavior	
1. The Senate in its report 103-143, page 95 stated... "The Committee urges NICHD to provide significant priority to research on normative behavioral development of ethnic minorities. The Committee recognizes that a long term commitment to this research is necessary to establish a comprehensive data base in order to evaluate the effectiveness of early educational interventions and other childhood programs."	1. Minority children constitute a rapidly growing segment of the population, and the scientific documentation of their normative development and conditions that influence it are important and need to be investigated. In January 1993, the NICHD awarded grants to five investigators who responded to a Request for Applications about the normative behavioral development of ethnic minorities. The NICHD also funds research on the development of minority children through its investigator initiated research program and through the support of the NICHD Study of Early Child Care that follows the development of 253 minority children from birth through age seven.
Rehabilitation Research	
2. The Senate in its report 103-143, page 95 stated..."The Committee has provided sufficient funds for the NICHD to increase funding for the National Center for Medical Rehabilitation Research [NCMRR] which is now in its second year of operation. This past fall, the Center awarded its first research grants, adding to the 13 research training grants previously funded...Future Center activities will be shaped in part by the research plan and report developed and submitted to Congress as was required by the legislation establishing the NCMRR."	2. The NICHD is pleased with the progress of the new National Center for Medical Rehabilitation Research. In FY 1993 the Center obligated a total of $9,995,000 in extramural funding. The FY 1994 Appropriation for the NCMRR is $14,000,000. This represents an increase of 40 percent over the FY 1993 level.

Item	Action Taken or to be Taken
Native American Initiative	
3. The Senate in its report 103-143, page 96 stated..."The Committee understands that certain areas served by the Indian Health Service have excessively high rates of infant mortality. The Committee encourages NICHD to implement a new research program to address effective interventions to prevent infant mortality in native American communities and urges the Institute to work closely with the Indian Health Service and tribal governments in the conduct of this study."	3. The highest rate of infant mortality of all Indian Health Service Areas is in the Aberdeen Area in South Dakota, where it averages 20 per 1,000 live births, and where rates in excess of 35 per 1,000 live births have been reported. The NICHD, the Aberdeen Area Indian Health Service, the Centers for Disease Control and Prevention, and the Aberdeen Area Tribal Chairmen's Health Board are conducting a study of infant mortality in the Aberdeen area to: accurately identify the causes of infant death; obtain information about medical, environmental, and social factors that may be responsible for the high rate of infant death; and establish a stable system for public health surveillance and support of families experiencing an infant death. The information obtained from this study will be used to design effective interventions. The steering committee for this study, which includes representation from IHS, NICHD, and CDC, will meet this year to review the progress and difficulties that have occurred over the first half of the projected study enrollment. Based on the findings, the committee will finalize plans for expansion to other reservations within the Indian Health Service for the next fiscal year.
Sudden Infant Death Syndrome	
4. The Senate in its report 103-143, page 96 stated..."Sudden infant death syndrome [SIDS]	4. In FY 1994 NICHD will continue with studies on the association of infant sleep position and

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Item	Action Taken or to be Taken
accounts for 7,000 to 8,000 infant deaths per year in the United States and is the Nation's leading cause of death among infants 1 month to 1 year of age.. ongoing studies in high-risk populations should be expanded in order to accelerate the acquisition of information. The Committee also commends NICHD for their initiation of a plan for the next 5 years."	SIDS infant physiology under different sleep conditions, the contribution of environmental factors like bedding and heating to SIDS, and a multicenter clinical trial of apnea monitors. The Institute is also planning studies to understand how the brain abnormalities observed in SIDS infants originate, and to develop methods to detect the abnormalities in infants before death.
Cystinosis	
5. The Senate in its report 103-143, page 96 stated..."The committee commends NICHD for its commitment to cystinosis research and looks forward to further progress on this debilitating condition.	5. Nephropathic cystinosis is a multisystem disease due to massive intracellular accumulation of cystine resulting from impaired transport. The disease is characterized by renal failure at approximately 10 years of age, renal tubular fanconi syndrome in infancy, growth impairment and photophobia. The NICHD through its intramural and extramural programs, continues to pursue basic and clinical research on this disease. In the intramural program, over 100 patients with cystinosis are receiving care. Cysteamine eyedrops have dissolved corneal crystals in young children and removed the haziness from the eyes of older children. Currently, linkage studies are being done to determine the chromosomal location of the cystinosis gene. In addition, an extramural study is currently investigating the visual processing deficit in children and adults with cystinosis.

Item	Action Taken or to be Taken
Mental Retardation and Developmental Disabilities	
6. The Senate in its report 103-143, page 96 stated..."The mental retardation research centers at NICHD pursue research that will lead to the full understanding of the causes of mental retardation and other developmental disabilities, the needs of people with mental retardation and developmental disabilities, and ways to reduce the incidence of these disabilities. Within the increase provided for NICHD, the Committee believes that the efforts of the mental retardation research centers should be expanded.	6. The NICHD currently supports 14 mental retardation research centers which form our nation's major research enterprise for the investigation of the various aspects of mental retardation and developmental disabilities (MRDD). Through cost-effective core laboratory services, fostering collegial interactions, and support of young investigators, these centers continue to improve our understanding of the causes, pathophysiology, diagnosis, treatment, amelioration and prevention of MRDD.
Pediatric Positron Emission Tomography (PET) Research	
7. The Senate in its report 103-143, page 96 stated..."The Committee encourages the Institute to expand support for research regarding the diagnostic applications of positron emission tomography in children and to utilize the expertise of PET facilities dedicated to the treatment of children's diseases and affiliated with other medical research and teaching institutions."	7. Non-invasive imaging techniques will play a major role in the early identification and correction of birth defects and in the diagnosis of genetic disease. Techniques of interest include Positron Emission Tomography (PET) Scanning, Magnetic Resonance Imaging (MRI), Computer Assisted Tomography (CAT) Scanning, and Ultrasound Imaging. The goal is to modify these techniques so that they can be used to image embryos and, ultimately, to produce 3-D images that demonstrate the progression of embryonic development. The NICHD is also interested in the creation of a data base of 3-D digital images produced by existing techniques. The images will be stored in a way that

Item	Action Taken or to be Taken
	enables them to show the 3-dimensional structure of organs and organ systems at individual embryonic stages, and the progressive changes that these systems undergo as development proceeds. They will be in a form that can be disseminated, retrieved and manipulated by the end users. These techniques and data bases will be used to help interpret experimental, genetic and teratological conditions and to diagnose, prevent and treat human birth defects and disease processes.
Demographic Research	
8. The Senate in its report 103-143, pages 96 & 97 stated..."Recognizing that demographic research provides the foundation of understanding from which informed public policy can be made, the Committee intends that NICHD continue to support demographic research. The Committee encourages research initiatives aimed at understanding how demographic factors affect the most vulnerable segment of our society -- children, minorities, women, and the oldest old. An expansion of the number of population research centers is desirable to facilitate the continuation of demographic research."	8. Demographic and behavioral Sciences research is a high priority of the NICHD. Many new initiatives in this area are being pursued. Last year the Family and Child Well-Being Research Network was established. This network comprises 7 outstanding scientists who are using existing data to study the relationship of family factors to outcomes for children. In addition, a request for applications has been issued to support research on the social, behavioral and cultural factors affecting child health in Hispanic populations. With regard to the population research centers, the FY 1995 request includes funds to increase the number of these projects from 10 to 11.

Item	Action Taken or to be Taken
Developmental Disabilities Prevention Research Center	
9. The Senate in its report 103-143, page 97 stated..."Within the increase for NICHD, the Committee has provided sufficient funds for the creation of a Developmental Disabilities Prevention Research Center within a university affiliated program [UAP], which shall investigate the critical problems of prevention and amelioration of mental retardation, specifically including: a specialized research center engaged in the X analysis of myelinogenesis as a critical period that is highly vulnerable to nutritional status during fetal and postnatal brain development. Priority emphasis shall be on experimental models which facilitate analysis of the molecular and cellular mechanisms of vulnerability and the potential for nutritional rehabilitation..."	9. The NICHD is now developing a request for applications to establish an additional specialized research center within a university affiliated program to prevent developmental disabilities due to disruption of normal brain development. Primary research emphasis will be on experimental models that will facilitate analysis of the molecular and cellular mechanisms of vulnerability and the potential for nutritional rehabilitation.
Endometriosis	
10. The Committee is pleased with the initial progress NICHD has made on biomedical research on endometriosis and fibroid tumors. The Committee remains very concerned, however, that little is known about the causes and natural history of these conditions.... Therefore, the Committee has provided sufficient funding within the budget of NICHD to significantly increase its research on endometriosis and fibroid tumors.	10. Endometriosis occurs in 5-15 percent of reproductive aged women and is found in 30-50 percent of women undergoing surgery for infertility. Women with endometriosis experience progressive pain and significant health care costs. A group of investigators have found that endometriosis patients, particularly those with mild disease or primary infertility, had abnormal tissue patterns of proteins, called integrins, involved in cell attachment and tissue invasion processes. The integrin proteins under study

Item	Action Taken or to be Taken
	may lead to important markers useful for the diagnosis and/or treatment of endometriosis as well as provide a greater understanding of how wayward uterine cells implant and grow into lesions in inappropriate body locations. The NICHD plans, in conjunction with the NIH Office for Research on Women's Health, to undertake the lead role in convening a multi-institute sponsored conference to evaluate the current progress achieved and the future directions for priority initiatives to further accelerate progress on endometriosis research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amt. Authorized	1994 Appropriation	1995 Amt. Authorized	1995 Budget Estimate
Research and Investigation..	Section 301	42§241	Indefinite	$481,008,000	Indefinite	$498,477,000
National Institute of Child Health and Human Development..............	Title IV, Part E	42§285g	Indefinite		Indefinite	
National Research Service Awards....................	Section 487	42§288	$400,000,000	17,761,000	Such sums as necessary	18,259,000
Total, Budget Authority...				498,769,000		516,736,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Appropriation History

Year	Estimate to Congress	House Allowance	Senate Allowance	Appropriation [1]
1986	$293,084,000	$306,812,000 [2]	$323,071,000	$321,796,000
1986 Sequester				-13,838,000
1987 [3]	309,119,000	368,509,000	362,866,000	366,780,000
1988	322,032,000	405,673,000 [4]	408,334,000	396,811,000
1989	397,945,000 [5]	407,650,000 [6]	431,388,000	425,649,000 [7]
1990	417,064,000 [8]	448,493,000	450,593,000	449,087,000 [9]
1990 Sequester				-6,173,000
1991	461,473,000	488,282,000 [10]	480,645,000	478,956,000 [11]
1991 Sequester				-6,000
1992	520,584,000	524,661,000	523,826,000	518,251,000 [12]
1993	545,238,000	534,094,000	534,094,000	527,788,000 [13]
1994	542,357,000	555,195,000	555,195,000	555,195,000
1995	516,736,000 [14]			

[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Excludes $13,901,000 in NRSA training programs not considered.

[3] The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance spread the funding among the Institutes, including $2,186,000 for NICHD.

[4] Does not include funding for AIDS research. Consolidated at the Secretary's level.

[5] The 1989 request excludes funds for AIDS research and education ($20,443,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

[6] Excludes $14,738,000 in NRSA training programs not considered.

[7] Excludes enacted administrative reduction of $5,739,000.

8/ The 1990 request excludes funds for the National HIV program ($27,129,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

9/ Excludes enacted administrative reduction of $1,506,000.

10/ Excludes $16,562,000 in NRSA training programs not considered.

11/ Excludes enacted administrative reductions of $11,876,000 and $1,913,000.

12/ Excludes enacted administrative reductions of $180,000, $5,048,000 and $973,000.

13/ Excludes enacted administrative reductions of $4,273,000, $29,000 and $2,004,000.

14/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Research for Mothers and Children........	--	237,445	--	248,380	--	254,759	--	253,640	--	261,439	--	+7,799
Population Research...	--	125,844	--	135,368	--	129,364	--	132,691	--	140,783	--	+8,092
Medical Rehabilitation Research............	--	---	--	7,270	--	9,995	--	14,000	--	15,112	--	+1,112
Subtotal.........	--	363,289	--	391,018	--	394,118	--	400,331	--	417,334	--	+17,003
Intramural Research....	334	59,861	370	66,401	363	69,628	334	73,074	319	73,004	-15	-70
Research management and support..........	190	23,188	207	26,429	199	25,214	189	25,364	189	26,398	--	+1,034
Total obligations..	524	446,338	577	483,848	562	488,960	523	498,769	508	516,736	-15	+17,967
Unobligated balance lapsing..............	--	41	--	174	--	---	--	---	--	---	--	---
Total, budget authority.	524	446,379	577	484,022	562	488,960	523	498,769	508	516,736	-15	17,967

Note: Includes FTEs associated with AIDS Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

Justification

National Institute of Child Health and Human Development

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
562	$488,960,000	523	$498,769,000	508	$516,736,000	-15	+$17,967,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of Child Health and Human Development. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute of Child Health and Human Development (NICHD) is that component of the NIH which is responsible for conducting and supporting research on maternal and child health, the population sciences, and medical rehabilitation.

Research encompassed by these areas targets infant mortality; prevention of birth defects, including genetic diseases; learning disabilities; the development and evaluation of contraceptives and infertility treatments; mental retardation and developmental disabilities; pediatric, maternal and adolescent AIDS; developmental biology; vaccine development; fetal medicine; demographic and behavioral research; and enhancement or restoration of function in individuals with a physical disability.

Research supported and conducted by the NICHD is multi-disciplinary and ranges from studies using the latest tools of molecular biology to unravel the mysteries of human development, from conception throughout adulthood; to studies of the dynamics of human behavior; to research using bioengineering to develop materials or devices to restore or enhance function in individuals with physical disabilities.

This research is carried out by five administrative entities: the Center for Research for Mothers and Children, the Center for Population Research, the National Center for Medical Rehabilitation Research, the Division of Epidemiology, Statistics and Prevention Research, and the Division of Intramural Research.

The President's Appropriation request of $516,736,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NICHD during the past five years has been as follows:

	Amount	FTE
FY 1990	$415,203,000	466
FY 1991	446,379,000	524
FY 1992	484,022,000	577
FY 1993	488,960,000	562
FY 1994	498,769,000	523

Purpose and Method of Operation

The NICHD carries out its extramural programs in research for mothers and children, population, and medical rehabilitation through support of research project grants, center grants, other research grants, training grants and fellowships, and research and development contracts. In addition, the Institute supports an intramural research program that includes prevention research. The scientific and administrative management and other overhead items are funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1995 budget request for the NICHD totals $516,736,000. This amount represents an increase of $17,967,000, or 3.6 percent, over the FY 1994 appropriation.

The FY 1995 request includes support for 508 full time equivalent positions (FTEs). This is a reduction of 15 FTEs from the FY 1994 Appropriation of 523. It is expected that this reduction will be accomplished through attrition.

The NICHD budget request for research project grants is $273,612,000, an increase of $6,312,000 or 2.4 percent over the FY 1994 Appropriation. The request will support 927 noncompeting grants at an average cost of $220,773 and 335 competing grants at an average cost of $194,194. This compares to 960 noncompeting and 330 competing awards in FY 1994. Since NICHD is supporting more expensive new grants the average cost of competing grants increases by 5.0 percent.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

In research centers, 78 centers in FY 1995 are requested for $52,774,000. This represents an increase of one new center in the demographic and behavioral sciences over the FY 1994 Appropriation.

Funding for cooperative clinical research would be increased by 12.6 percent for a total of $23,561,000. This increase will fund an additional 3 cooperative clinical units of the Institute's reproductive medicine network to include clinical trials of new treatments for gynecologic disorders such as fibroids and endometriosis. The increase will also provide additional support for existing cooperative clinical units in maternal-fetal medicine, neonatal intensive care, and sudden infant death syndrome.

The request for R&D contracts is $37,542,000, an increase of $4,411,000 or 13.3 percent over the FY 1994 level. The increase includes funds to maintain the current level of effort in existing programs, additional funding for breast cancer research, and funds to support the Institute's Perinatology Research Branch located at Georgetown University in Washington, D.C.

In research training, the Institute will support 750 full-time equivalent trainees in FY 1995 for $18,259,000. This is the same number of trainees and an increase of $498,000 over the FY 1994 Appropriation.

In intramural research and research management and support, FY 1995 funding levels are $73,004,000 and $26,398,000, respectively. In both programs, mandatory cost increases are offset by program decreases and decreases associated with reduced full-time equivalent FTE employment levels in FY 1995.

National Institute of Child Health and Human Development

Extramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$394,118,000	$400,331,000	$417,334,000	+ $17,003,000

The extramural research programs of the NICHD is comprised of the following budget activities: Research for Mothers and Children, Population Research, and Medical Rehabilitation Research.

Funding for the NICHD extramural research programs during the past five years has been as follows:

	Amount
FY 1990	$338,676,000
FY 1991	363,289,000
FY 1992	391,018,000
FY 1993	394,118,000
FY 1994	400,331,000

Rationale for the Budget Request

The FY 1995 request for the NICHD extramural programs is $417,334,000, an increase of $17,003,000 over the FY 1994 level. With the FY 1995 extramural request, these funds will provide support for the following activities: Research for Mothers and Children, $261,439,000, an increase of $7,799,000 or 3.1 % over the FY 1994 estimate of $253,640,000; Population Research, $140,783,000, an increase of $8,092,000 or 6.1 % over the FY 1994 estimate; and Medical Rehabilitation Research, $15,112,000, an increase of $1,112,000 or 7.9 % over the FY 1994 estimate of $14,000,000. Examples of recent accomplishments, current program activities, and future plans are described below.

RESEARCH FOR MOTHERS AND CHILDREN

The Center for Research for Mothers and Children (CRMC), one of the three extramural divisions of the National Institute of Child Health and Human Development, is the primary focus of support for research and research training concerning maternal and child health at the National Institutes of Health. Biomedical and behavioral research programs supported by the CRMC extend from conception to maturity. These programs are designed to advance the goal of ensuring the birth of healthy babies who have the opportunity to reach adulthood unimpaired by physical or mental disability and, therefore, able to achieve their full genetic potential. The CRMC has a special interest in programs designed to prevent prematurity, low birth weight and Sudden Infant Death Syndrome, conditions which are related to infant deaths in the U.S. Other CRMC research programs have as a goal the prevention or amelioration of birth defects, mental retardation, learning disabilities, pediatric AIDS, childhood injury, and other conditions which impede optimal physical or behavioral development. The CRMC also supports studies of normal physical, cognitive, psychological and social development to understand these processes and identify what may interfere with optimum growth and development. Knowledge acquired from these studies will be used to design more effective intervention strategies.

Infant Mortality and Morbidity: A large study supported by NICHD has shown that there is no health benefit derived from routine screening with ultrasound in low risk pregnancies. The investigators estimate that up to $1 billion could be saved each year in the U.S. if ultrasound examinations were limited to high risk pregnancies or when problems arise.

The NICHD Neonatal Intensive Care Unit (NICU) Network is conducting several studies which will improve the outcome and decrease the cost of care of very low birth weight infants. These include a study assessing the effectiveness of steroids in preventing chronic lung disease in infants with respiratory distress syndrome (immature lungs) and a study to determine if giving phenobarbital to pregnant women at risk for premature delivery will prevent brain hemorrhages in their infants. In a study recently concluded by the NICU Network, it was found that antenatal steroid administration is associated with striking reductions in the risk of mortality and morbidity (brain hemorrhage, respiratory distress syndrome, and chronic lung disease) in very low birth weight infants.

NICHD, in a collaborative effort, is conducting a large interdisciplinary study of the sequelae of intrauterine drug exposure. Sixteen thousand women will be enrolled and 4,000 infants will be followed for 3 years to assess acute and long-term development and the life circumstances of these infants and their families, including service requirements, quality of parenting, ongoing drug exposure, the role of violence, and lead exposure. The infants will be assessed for subtle cognitive, social, and language developmental disabilities. The findings will lead to interventions to improve the developmental outcome of these infants.

The NICHD five-year research plan for SIDS is directed toward acquiring knowledge to identify infants at risk for SIDS and to prevent SIDS deaths. In Fiscal Year 1994 the NICHD is releasing a request for grant applications to understand how the brain abnormalities observed in SIDS infants originate, and to develop methods to detect the abnormalities in infants before death.

The Maternal-Fetal Medicine Unit (MFMU) network has completed a randomized clinical trial on the use of low dose aspirin as a means of prevention of preeclampsia in low risk patients. Although there was a slight reduction in preeclampsia in the group receiving aspirin, there was no improvement in perinatal outcomes and some increase in risk. The investigators concluded that the benefit is insufficient to justify aspirin use in low risk patients at this time.

Bionutrition: The NICHD supports bionutrition research designed to increase understanding of nutrient function at the cellular and molecular levels. Preliminary studies have shown a strong relationship between low maternal zinc levels and decreased fetal growth. On the basis of these findings the NICHD is currently funding a randomized clinical trial of zinc supplementation in pregnancy in 600 black women. Its goal is to reduce preterm birth, growth retardation and perinatal infection, outcomes which are associated with poor zinc nutriture. The trial is being conducted in black women with low zinc levels because that population currently has twice the rate of low birthweight and twice the rate of neonatal mortality of the general U.S. population.

Pediatric Pharmacology Research Units: Modern pediatric pharmacology is a sophisticated clinical discipline, capable of carrying out the studies necessary for the safe and ethical evaluation of drugs in children. The NICHD has initiated a new network of Pediatric Pharmacology Research Units (PPRU) in order to provide resources for elimination of the problem of the therapeutic orphan, a situation in which more than three quarters of the drugs marketed in the United States, including many of the most useful agents in modern therapy, are not approved as safe and effective for use in children. The objective of this program is to increase the number and variety of medications that are approved for use in children, with the ultimate goal that all drugs prescribed for children be labeled for such usage.

Birth Defects: Birth defects account for more than 20 percent of infant deaths, making them the leading cause of infant mortality in the United States. Even if they are not lethal, birth defects impact enormously on the physical and emotional health of affected children and their families. Basic research and innovative technology provide new avenues to knowledge needed for meaningful therapy and prevention. Genes that are developmentally important and relevant to human disease are now being identified and characterized through animal models in combination with human studies. Ongoing research is defining how genetic cascades regulate cell proliferation, cell differentiation, cell interactions and cell fate. The roles of environmental agents and nutritional factors are also being investigated. These studies can provide a systematic approach to understanding the networking of genes and gene families, the mechanisms of development, the determination of critical developmental periods and the identification of genetic and environmental miscues that give rise to such conditions as neural tube defects, skeletal abnormalities, and congenital megacolon among many others.

Mental Retardation and Developmental Disabilities: The NICHD supports 14 Mental Retardation Research Centers (MRRCs) which form our nation's major research enterprise for the investigation of the various aspects of mental retardation and developmental disabilities. Through cost-effective core laboratory services, fostering collegial interactions, and support of young investigators, the MRRCs continue to improve our understanding of the causes, pathophysiology, diagnosis, treatment, amelioration and prevention of mental retardation and developmental disabilities.

Rett Syndrome: Rett syndrome is a neurological disorder affecting young girls at a frequency of about 1/15,000 births. The syndrome results in arrested development of motor and social skills, followed by further loss of neurologic function, seizures, and curvature of the spine, ultimately leaving the patient totally helpless. Current research is focusing on the molecular genetic basis, and possible strategies for diagnosis and treatment of this disorder. NICHD is currently supporting two large program projects on Rett syndrome.

Study of Early Child Care: The NICHD has initiated a 10 site study of 1,364 families who had a baby in 1991. The goal of the study is to explore how variations in early child care experiences -- age of entry to child care, number of hours in care, quality of care -- influence the cognitive, language, social, emotional and health development of children. While the study was originally scheduled to follow the children through age three, the NICHD has decided to extend the follow-up through age seven, with special emphasis on the transition to school, an important milestone in children's development.

POPULATION RESEARCH

The NICHD's Center for Population Research (CPR) is responsible for the primary Federal extramural effort in population research. CPR carries out its programs through the support of research and research training in the biomedical, demographic and behavioral sciences. Funding is provided through grants and contracts for fundamental biomedical research in the reproductive sciences relevant to problems of human fertility and infertility, the development of safe and effective methods for fertility regulation, the evaluation of the benefits and risks of current contraceptive methods, and demographic and behavioral sciences research on the causes and consequences of population structure and change.

Demographic and Behavioral Sciences: The demographic and behavioral sciences program supports research on the size, rate of growth, and composition of our Nation's most valuable asset, its population. The topics addressed include factors affecting changes in patterns of birth, death, and migration; family structure; the growth and changing characteristics of our population; and the relationship of these variables to individual, familial, and societal well-being.

A comprehensive analysis of how families affect the well-being of children will be undertaken by a new research network established by NICHD. The Family and Child Well-Being Research Network comprises 7 outstanding scientists who are using existing data to study the relationship of family factors -- for example, single parent families, child support, parenting practices -- to outcomes for children. The Network has two central goals: to systematically exploit existing data resources to produce sound scientific answers to public policy questions, and to promote the development of interdisciplinary research linking family factors to the well-being of our nation's children.

Immigration has profound implications for the health of our nation's people. As the fundamental cause of our increasing ethnic and racial diversity, it contributes directly to the cultural beliefs and behaviors affecting health and use of health services. Recent research suggests that attempts to control illegal immigration through legislation have fallen short of their goals. Investigators studying immigration patterns between Mexico and the United States have found that the level of illegal immigration remains high despite high rates of apprehension by border police. The study suggests that arrest at the border blocks only a single attempt to cross, but does not deter future attempts to enter the United States. These results reinforce the need for better research addressing the social, economic and health impacts of immigration on the United States as well as on our Mexican neighbors. Results from the same study suggest that rural communities in Mexico may be highly dependent on funds transferred from relatives in the United States, and that this dependency may actually be altering the structure of incentives for economic development in these rural communities.

One of the most comprehensive studies to date of the sexual behavior and condom use of adult U.S. men revealed rates of condom use ranging from 25 percent among white men to 38 and 39 percent, respectively, among African-American and Hispanic men. Even within high-risk populations, fewer than half of men reported recent condom use. In addition, the study examined beliefs and attitudes about condoms and identified important barriers to increasing use including concerns about condom breakage and reduced sensation, embarrassment, and the perception that condom use conveys negative messages about one's self or one's partner. The study also collected information on sexual behavior to measure risk for sexually transmitted disease. These data confirmed the results of other national surveys in finding a prevalence of male homosexuality substantially lower than previously estimated on the basis of the Kinsey studies. Further analysis of the data collected in this study will develop behavioral models of condom use to inform design of intervention programs.

For black youth between the ages of 15 and 24, violence is the leading cause of death. To design better measures to prevent this growing epidemic of violence, NICHD researchers are trying to enhance their theoretical understanding of such fundamental issues as 1) what constitutes developmental norms in ethnic minorities; 2) how different styles of child rearing influence normal development as well as aggressive behavior and 3) what is the effect of domestic violence on children's development. Such basic behavioral research provides the basis for developing and evaluating interventions to reduce violence and violent-elated behaviors in youth. With funds from the Office of Minority Health, NIH, the Institute supports a large initiative targeted to the needs of different ethnic and racial communities, to reduce a variety of risk-taking behaviors, including violence.

Contraceptive and Reproductive Evaluation: The Institute supports research on the medical effects of contraceptive drugs, devices, and surgical procedures that are available in the United States. Investigations on the role of non-contraceptive gynecological products or procedures in reproductive disease etiology or prevention; the benefits and risks of marketed exogenous gonadal steroids, including oral contraceptives, postmenopausal hormones, and fertility drugs; and the role of barrier contraceptives in disease prevention as well as contraception are also studied.

Two NICHD-supported studies of the long-term effects of vasectomy were published this year. One study followed vasectomized and non-vasectomized men for an average of eight years and concluded that vasectomized men had no higher risk of the many diseases studied, other than inflammation of the epididymis early after the procedure. This project, however, was not able to study diseases occurring primarily in older men, such as prostate cancer. Another project supported by NICHD suggested that vasectomized men may be at higher risk of prostate cancer. These findings and those from previous and ongoing studies were reviewed at an NICHD conference in March 1993, which concluded that while vasectomy has not been shown to cause prostate cancer, further investigation is needed to answer this question definitively. NICHD is currently planning a case-control study designed to address this issue.

During the past year several reports have been published linking ovarian cancer with the use of some drugs commonly used in infertility treatment to stimulate the ovary. Because these drugs are used by so many women (including some women who are not infertile themselves but are donating eggs), NICHD is launching a cohort study to determine whether fertility drugs increase the risk of ovarian cancer.

The FDA recently approved the female condom as a female-controlled barrier contraceptive device that offers protection against sexually transmitted diseases. Since this approval was expedited to provide a needed device to the public, FDA requested NIH to conduct post marketing studies. In response to this request the NICHD is designing an observational clinical trial to evaluate the protection afforded by the female condom for protection from gonorrhea and chlamydia. Participants in the study will each be followed for six months. In addition to determining rates of infection among users relative to nonusers, this study will also compare infection rates between women relying on the female condom to women relying on the male condom for protection.

Contraceptive Development: The contraceptive development program supports clinical trials and laboratory studies aimed at developing and improving methods of fertility regulation for both men and women that are safe, effective, reversible, and acceptable to various population groups. Research goals include the development of new drugs and devices to regulate fertility in both sexes, improved methods of drug delivery, better barrier methods of contraception, and prevention of transmission of sexually transmitted diseases including the AIDS virus.

The three contraceptive research centers supported by the NICHD are making progress on several fronts. Two of the centers focus on contraceptive vaccine development. At least ten candidate proteins have been isolated, are being produced in large quantities, and are being injected into animals to assess their effectiveness at preventing fertilization. Such studies have already begun in female baboons and have resulted in a reduction of fertility. Other trials of different antigens will be conducted in the coming year. Investigators in the contraceptive research centers are also developing a contraceptive ring that can be inserted in the vagina. Preliminary clinical trials indicate that although the device delivers one-third less hormone than conventional oral contraceptives, it is every bit as effective and nearly free of side effects. Additional trials are planned to confirm the device's safety, effectiveness and acceptability.

Independent of the contraceptive research centers program, a contraceptive vaccine for men is being developed. Enough preliminary safety and efficacy studies in animals have been completed so that immunization studies of men have begun.

In the past two years, the NICHD has initiated programs to develop new and to improve existing physical barrier methods of contraception that will also allow women and men to protect themselves against sexually transmitted infections, including the AIDS virus. Preliminary reports from clinical evaluation of new condoms made of polyurethane have shown that they have very low breakage and slippage rates and are preferred over the latex condom. A spermicide-releasing disposable diaphragm with the potential for high efficacy and acceptability has also entered clinical testing. A new cervical cap is also being created.

Reproductive Sciences: The major goal of the Institute's reproductive sciences research program is to actively promote and support "bench to bedside" research and research training aimed at developing new knowledge in reproductive medicine that will advance clinical applications in infertility alleviation, fertility regulation, and the diagnosis or treatment of fertility impairing reproductive disorders.

Infertility affects about 8 percent of U.S. couples with up to one-half of these couples (nearly 2.2 million in the U.S.) not able to achieve their fervent desire to have a baby. Infertility in the U.S. has both a tragic, often devastating, impact on young couples desiring to build a family and a significant impact on the medical economics of health care provision in the U.S. It is known that up to 40 percent of infertility may be due to disorders of ovulation in the female.

In a study supported under the NICHD Infertility Research Centers, a six-cycle treatment comparison of standard exogenous gonadotropin hormone injections versus a micropump means of intravenously administering pulsatile Gonadotropin-releasing hormone (GnRH) to induce natural (endogenous) gonadotropin secretion resulted in an increase of conceptions from 72 percent to at least 96 percent. In addition to lower treatment cost, the newer procedure had significantly fewer multiple baby pregnancies. In an associated study, the marked increase of medical costs associated with an increasing number of babies born to a mother during hospitalization for a multiple gestation pregnancy has been determined to grow by significant jumps from one baby ($3,666), to two babies ($6,277) and three or more babies ($13,357). These findings demonstrate that the development of procedures that limit the occurrence of treatment-induced multiple births could have a marked national impact on the associated medical, social, and economic costs in this health care area. Research aimed at attaining this goal continues in these centers.

Endometriosis is a poorly understood condition characterized by cells from the uterine lining growing in other body locations. It occurs in 5-15 percent of reproductive aged women and is found in 30-50 percent of women undergoing surgery for infertility. Women with endometriosis experience progressive pain and significant health care costs. As part of the 1992 initiative on endometriosis and myomas, a group of investigators have found that endometriosis patients, particularly those with mild disease or primary infertility, had abnormal tissue patterns of proteins, called integrins, involved in cell attachment and tissue invasion processes. The integrin proteins under study may lead to important markers useful for the diagnosis and/or treatment of endometriosis as well as providing a greater understanding of how wayward uterine cells implant and grow into lesions in inappropriate body locations.

Up to 40 percent of infertility in the human is associated with male factors. Male infertility is currently not well understood. In addition to the poorly understood qualitative factors whose abnormalities contribute to male infertility, recent reports of a widespread decline in sperm counts have raised the question of whether this phenomenon has contributed to male infertility. As very few couples with a female of normal fertility have a readily identifiable or treatable problem such as male hypogonadism, the empirical use of costly assisted reproductive technologies, including hormonal enhancement treatment of the female, has been widely practiced. The current status of treating male fertility problems is discouraging with some reports indicating only a 20 percent success rate in fathering a child over a 2 year treatment plan. The NICHD recently held a workshop on male spermatogenesis and is developing an initiative on idiopathic (unexplained) male infertility designed to accelerate research in this important area of reproductive health.

MEDICAL REHABILITATION RESEARCH

The mission of the National Center for Medical Rehabilitation Research (NCMRR) is to foster development of the scientific knowledge needed to enhance the health, productivity, independence and quality of life of persons with disabilities. This is accomplished by supporting research on the restoration, replacement, or enhancement of functioning required by people with disabilities to be effective in daily life. Disability has a major impact (exceeding $200 billion annually) on the U.S. economy, and it can have devastating effects on the 35 million persons with disabilities, as well as on their families and communities. As the organizational focus for medical rehabilitation research at the NIH, the NCMRR provides funds for research and research training, facilitates coordination of relevant research within the NIH and other agencies, and disseminates information to scientists, rehabilitation service providers, and to persons with disabilities and their families.

Morbidity/Mortality or Epidemiology: Available survey data do not meet the needs of health planners for information about the growing population of persons with disabilities. The NCMRR has provided support to the National Center for Health Statistics to supplement information yielded by the National Health Interview Survey. National estimates will be obtained about the prevalence of various types of disabling impairments and about how these conditions influence the lives of people with disabilities.

Sociosexual Adaptation of Women with Physical Disabilities: Little is known about impacts of the disabling process on the sexuality of the more than 20 million women in this country with physical disabilities. The NCMRR is supporting a survey study of how these women view themselves as sexual individuals and of their success in establishing intimate relationships. Initial results indicate that women with disabilities experience a much higher level of abuse than was anticipated and that they encounter numerous societal barriers to normal sexual development.

Bowel and Bladder Management: Difficulties with bowel and bladder functioning are chronic and frequent health problems for many individuals with a physical disability. Studies are being supported to improve bowel and bladder management by developing alternatives to currently used procedures which are time consuming, variable in their effects, and associated with a substantial risk of infection.

Decubitus Ulcers: Annually, an estimated 1,000,000 people or more develop skin sores that do not heal rapidly. The aggregate human and monetary costs of these chronic wounds are significant. The Center issued a Request For Applications (RFA), "Skin Integrity and Assistive Devices," that will provide funds to develop new methods of enhancing wound healing. Recently, the NCMRR co-funded a trans-NIH RFA on chronic wound healing in the skin to identify the underlying pathophysiology and to provide biological bases for new treatment interventions. Currently, the NCMRR is funding an SBIR grant to establish standards for bedding and mattresses that will reduce the probability that people who are immobilized will develop skin breakdown.

Neurorehabilitation: Many disabling conditions involve damage to the nervous system. Such injuries can dramatically impair both motor and cognitive skills. Research is urgently needed to examine mechanisms in the nervous system that are capable of restoring or enhancing the functioning of persons with longstanding injuries of the brain or spinal cord. The NCMRR will launch an initiative to stimulate research on the innate plasticity of the nervous system in persons with chronic injuries of the central nervous system.

National Institute of Child Health and Human Development

Intramural Research

Authorizing Legislation - Sections 301 and 487 of the Public Health Service Act. 1994 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
363	$69,628,000	334	$73,074,000	319	$73,004,000	-15	-$70,000

The NICHD Intramural Research Program is comprised of the Division of Intramural Research and the Division of Epidemiology, Statistics and Prevention Research. The Division of Intramural Research conducts laboratory and clinical research on reproduction and on the biomedical and behavioral aspects of human development. The Division of Epidemiology, Statistics and Prevention Research is responsible for the coordination of the Institute's programs related to health promotion and disease prevention.

Funding for intramural research during the past five years has been as follows:

	Amount	FTE
FY 1990	$53,222,000	279
FY 1991	59,861,000	334
FY 1992	66,401,000	370
FY 1993	69,628,000	363
FY 1994	73,074,000	334

Rationale for the Budget Request

The FY 1995 request for intramural research is $73,004,000, a decrease of $70,000 from the FY 1994 appropriation of $73,074,000. The following are recent accomplishments, current activities, and future plans.

LABORATORY AND CLINICAL RESEARCH

Scientists in the Division of Intramural Research will continue to pursue promising leads that are broadly concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. The key to the prevention of common "adult" diseases, such as cancer, heart disease, mental illness, immunologic disorders, and premature aging, lies in our understanding of the rules which govern early development. Research is carried out in patients as well as in a diversity of animal models. Currently, two themes of basic investigation are being emphasized throughout the program: The structure, function, and transmission of genes -- knowledge in this area is critical as we embark upon an era of "gene therapy" -- and "signal transduction", the complex pathway by which environmental stimuli induce a signal at the cell surface which eventuates in the expression of genes in the nucleus. There is also an intensive effort in vaccine development, particularly with respect to common but serious bacterial infections of children, and a major emphasis on the development of new methods and tools of interest to biotechnology.

Perinatology Research Branch: The intramural Perinatology Research Branch was established in 1992 to conduct research on pregnancy and perinatology that addresses the most important causes of premature delivery and infant mortality. Last year, a permanent site for the clinical and laboratory research of the Branch was established at Georgetown University in collaboration with Howard University and D.C. General Hospital, and a support contract was awarded to begin to provide facilities for this Branch. This year, the new Branch expects to become fully operational and is currently outfitting the new facilities so that it may vigorously pursue its research objectives.

Inborn Errors of Metabolism: Intramural scientists have isolated the gene that is defective in children suffering from a serious inherited error of metabolism. The disorder, Glycogen Storage Disease Type 1A --"von Gierke's disease,"-- causes enlargement of the liver and kidneys and often severely impairs a child's physical and, if untreated, mental development. Affected children are usually diagnosed in infancy, but there is no cure for this disease. This advance will make genetic counseling much more effective — it will make it easier for doctors to tell if a prospective parent carries the abnormal gene. It will also simplify the diagnosis of children who suffer from the disease—a blood sample will now suffice rather than a liver biopsy. The next step is to use this information to develop gene therapy for affected infants and children.

Familial Male Precocious Puberty (FMPP): In normal boys, the brain's pituitary gland signals the testes when to start making adult amounts of the male sex hormone, testosterone. Testosterone is the hormone that causes all of the signs of puberty—enlargement and maturation of the sexual organs, growth of body hair, deepening of the voice, etc. In boys with familial male precocious puberty (FMPP), the testes seem to start "going it alone"—pouring out testosterone without waiting for the go-ahead from the brain. These children, some as young as two years old, have as much testosterone in their blood stream as adults, which is what causes them to enter puberty so early. Now scientists in the NICHD, with their collaborators in the NIDDK, have found that there is a genetic error in the receptor ("LH") that receives the pituitary signal in the testes cells that are responsible for manufacturing testosterone. This error causes the receptor to behave as if it were jammed in the on-position. With this error, the internal structure of the receptor is subtly altered, so that the signalling pathway of the cell is irreversibly switched on. FMPP is the first example of an inherited human disease caused by such an activating mutation in this type of receptor, but it is likely that a number of other human diseases may be caused by similar mutations.

Plant Polysaccharides as Human Vaccines: Of the types of bacteria which cause the most serious -- and often life-threatening -- infections in infants and children, many are surrounded by an antigenic capsule composed of complex polysaccharides. These capsular polysaccharides (CPS) endow the organisms with virulence, but they also induce protective antibodies in the host which they infect. However, these CPS antigens are weak; while they are reasonably effective in adults, they are ineffective in infants and young children (who have a less mature immune response). Intramural scientists discovered some years ago that if purified CPS is chemically conjugated to a highly immunogenic protein, e.g., tetanus toxoid, even infants will mount a strong immune response not only to the protein but to the CPS as well. This discovery ushered in a new generation of powerful vaccines for the prevention of serious bacterial infections at all ages, but especially in infants and young children. Recently, these same scientists noticed that pectin, a plant polysaccharide -- from citrus fruits -- is structurally very similar to "Vi", the CPS antigen of *S. typhi*, the causative organism of typhoid fever. When injected into mice, native pectin does not induce antibodies to Vi. However, if pectin is modified by a simple chemical procedure that makes it even more similar to Vi and is conjugated to tetanus toxoid, it is as effective as the Vi conjugate in eliciting anti-Vi antibodies when injected into mice. It is likely that many other structurally similar and antigenically cross-reactive polysaccharides may serve as human vaccines. Such plant-based vaccines would be more readily standardized and have a greatly increased yield as compared with polysaccharide antigens obtained from bacteria *per se*. Therefore, plant vaccines would be far easier and cheaper to produce.

Shigella sonnei and Shigella flexneri - Despite a century of intensive study, there are no licensed vaccines for these common and serious intestinal pathogens, which remain major causes of morbidity among children throughout the world, including arrested growth and mortality. NICHD scientists have synthesized three Shigella conjugates that have been shown to be safe and elicit serum antibodies in adults. With continued research, NICHD scientists plan to test these conjugates for co-administration with DPT in infants, to provide the earliest possible protection and simplicity of scheduling.

EPIDEMIOLOGY, STATISTICS AND PREVENTION RESEARCH

The Division of Epidemiology, Statistics and Prevention Research conducts investigations to increase our understanding of determinants of perinatal and infant mortality, intrauterine growth retardation, preterm delivery, congenital malformations and normal growth and development. It is also responsible for the coordination of the Institute's programs related to health promotion and the prevention of disease. It fosters the maintenance and enhancement of health and well-being by transferring knowledge gained through prevention research to health care professions.

Calcium for Preeclampsia Prevention (CPEP): Preeclampsia is a disease of women which occurs in 5-10 percent of all pregnancies. It is manifested by hypertension and kidney damage. In severe cases, the blood clotting system, the liver, and the brain may also be affected. About one-fifth of all U.S. maternal deaths and one-fifth of all perinatal deaths are associated with maternal preeclampsia or hypertension. Because of its public health importance, the search for an effective preventive therapy has been a major focus of NICHD research.

A number of small clinical trials have indicated that preeclampsia may be prevented by supplementing the diet with inexpensive calcium tablets. Most of the trials were conducted in third world countries where, unlike the U.S., the usual dietary intake of calcium is low. Moreover, none of the trials has reported the outcome of systematic surveillance for important possible side effects of treatment, such as kidney stones. In response to the need for a definitive evaluation of the benefits and side effects of calcium supplementation to prevent preeclampsia in U.S. women, the NICHD is conducting a large trial at five university medical centers across the country. About 4500 pregnant women will be enrolled, half of whom will receive calcium supplements, and half, placebo. The trial includes large numbers of blacks and Hispanics.

The trial was started in June 1991. More than 2200 women have been enrolled to date. Enrollment is expected to conclude by March 31, 1995. The results will be reported during 1996.

District of Columbia Infant Mortality Initiative: The NICHD Infant Mortality Initiative is designed to examine factors associated with the well-being of mothers and infants and to test the effectiveness of interventions for reducing infant mortality and morbidity. This study supported by funds from the Office of Minority Health NIH, will be conducted on young families in the District of Columbia with a special focus on pregnant women, infants up to one year of age, and women in the childbearing age. The study group is currently examining the feasibility of interventions to increase participation in early prenatal care, to determine the relative impact of illicit drug use and other factors occurring with illicit drug use, such as poverty, on infant outcomes, and examining the effect of levels of perinatal care services on infant outcome. The overall goal of these studies is to reduce the high rate of poor pregnancy outcome in the District of Columbia.

Vitamins to Prevent Spina Bifida and Related Birth Defects: Spina bifida and other related defects -- neural tube defects or NTDs -- are among the most common birth defects. Many affected children die shortly after birth. Virtually all survivors are left with serious medical problems including paralysis, orthopedic problems and chronic infections. The cost, both in terms of medical care and years of life lost, is enormous. It has recently been shown that folic acid supplements can reduce the risk of NTDs. However, the mechanism by which folic acid works is unknown. NICHD scientists are currently studying women who have had affected pregnancies to identify the biochemical defect. If such a defect can be identified, it may make it possible to target a subgroup of women at risk for having offspring with NTDs. This would simplify efforts to provide supplements prior to pregnancy and reduce the cost of supplementation. This study may also help to focus prevention efforts by determining what aspect of folate metabolism is abnormal.

Diarrheal Research: Diarrheal infections caused by enterotoxigenic *Escherichia coli* (ETEC) have been estimated to cause nearly 1 million childhood deaths worldwide each year. Although these infections are seen primarily in less-developed settings, they also affect residents from developed countries. There is considerable interest in the development of anti-ETEC vaccines. Although no such vaccine exists at present, several oral vaccine candidates are being developed. DESPR investigators, in collaboration with the U.S. Navy, the University of Gotheborg, and the University of Alexandria, are conducting studies of the epidemiology of ETEC diarrhea in Alexandria, Egypt. In addition to providing the background data necessary for the design of ETEC vaccine trials, this work will prepare this site for the first trial of an oral killed ETEC vaccine in an ETEC-endemic area.

Neonatal Receipt of Vitamin K - Vitamin K is routinely administered to newborns in the U.K. to prevent hemorrhagic disease. However two recent studies in the U.K. have reported that intramuscularly administered vitamin K was associated with a twofold increased risk for childhood cancer. NICHD conducted a study of U.S. infants born during the period when vitamin K was introduced, comparing the cancer rates in the groups of infants who were and were not treated with vitamin K. Among the 54,795 children studied, there were 48 cases of cancer for each case, five controls were selected and the vitamin K exposure status of the cases and controls was ascertained. NICHD investigators found no association between exposure to vitamin K and any childhood cancer. These results are important because the benefits of vitamin K in preventing fatal hemorrhagic disease are well established. This study concludes that there is no reason to abandon the current practice of routine administration of vitamin K to all newborn infants.

National Institute of Child Health and Human Development

Research Management and Support

Authorizing Legislation - Sections 301, Title IV, Subpart 7
1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
199	$25,214,000	189	$25,364,000	189	$26,398,000	--	+ $1,034,000

The Research Management and Support (RMS) activity provides staff and resources for the administrative management and scientific direction of the Institute. Managerial and administrative services are provided through the following organizational components: the Office of the Director, the Office of Administrative Management, the Office of Research Reporting, the Office of Science Policy and Analysis, and the Office of Grants and Contracts. Scientific direction and administrative management of the Institute's extramural program is provided by the Institute's Scientific Review Program as well as program staff of the Institute's extramural activities.

Funding for the RMS program during the past five years has been as follows:

	Amount	FTE
FY 1990	$23,305,000	187
FY 1991	23,229,000	190
FY 1992	26,603,000	207
FY 1993	25,214,000	199
FY 1994	25,364,000	189

Rationale for the Budget Request

The FY 1995 request for RMS is $26,398,000, an increase $1,034,000 over the FY 1994 estimate of $25,364,000. During FY 1995, RMS activity will continue to provide for the professional leadership and technical guidance needed to plan, direct, and implement all programs of the Institute; and to conduct a broad program of information dissemination.

Some specific functions performed by the various components of this activity follow. The Scientific Review Program provides policy direction and coordination of review activities within NICHD involving extramural grant and contract awards. Additionally, this group serves as liaison for applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations. The scientific program staffs of the Center for Research for Mothers and Children, the Center for Population Research, and the National Center for Medical Rehabilitation Research concentrate their efforts on the scientific management of the Institute's grants and contracts and assist in the planning and development of new programs that will best accomplish the mission of the NICHD.

NATIONAL INSTITUTES OF HEALTH

National Institue of Child Health and Human Development

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	7	7	7
Office of the Deputy Director	2	2	2
Office of Administrative Management, Office of Research Reporting, Office of Science Policy and Analysis, and Office of Grants and Contracts	95	90	90
Center for Population Research	32	30	30
Center for Research for Mothers and Children	39	36	36
National Center for Medical Rehabilitation Research	8	8	8
Division of Scientific Review	17	16	16
Division of Epidemiology, Statistics, and Prevention Research	34	31	30
Division of Intramural Research	328	303	289
Total, NICHD	562	523	508

Average GS/GM Grade

1990	9.9
1991	9.8
1992	10.0
1993	10.4
1994	10.4
1995	10.4

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

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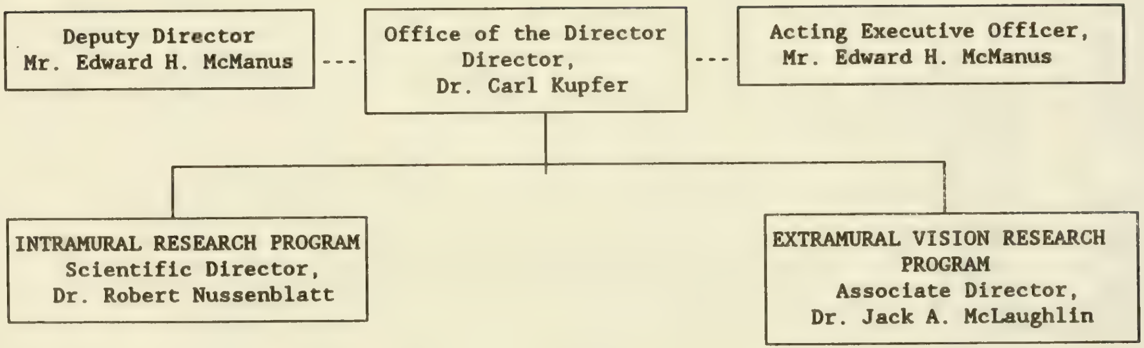
NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Eye Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to eye diseases and visual disorders, [$290,260,000] $292,022,000 *of which $3,150,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriations Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Language Analysis

Language Provision	Explanation
"....of which $3,150,000 shall not become available for obligation until September 19, 1995."	To ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation[1]

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation...........	$279,102,000	$290,260,000	$292,022,000
Section 511 .8% reduction...............	-2,233,000	---	---
Section 216 S&E reduction	-651,000	---	---
Section 513 consultant services reduction......	-30,000	---	---
Subtotal, adjusted appropriation.........	276,188,000	290,260,000	292,022,000
Real transfer to: NIAID for tuberculosis research...	-271,000	---	---
Comparative transfer to: Office of AIDs Research for HIV Activities......	-6,283,000	-8,381,000	---
Subtotal, adjusted budget authority......	269,634,000	281,879,000	292,022,000
Unobligated balance lapsing................	-549,000	---	---
Total obligations........	269,085,000	281,879,000	292,022,000

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[1] Excludes the following amounts for reimbursements activities carried out under this account: 1993 - $9,284,000; 1994 - $11,000,000; and 1995 - $12,000,000.

NATIONAL INSTITUTE OF HEALTH

National Eye Institute

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting.........	748	$141,036,000	680	$136,408,000	711	$151,154,000
Admin. supplemental..	(22)	1,947,000	(22)	1,400,000	(22)	1,458,000
Competing						
Renewals............	127	27,120,000	157	35,059,000	131	30,677,000
New.................	100	15,089,000	123	19,024,000	105	16,774,000
Supplemental........						
Subtotal, competing	227	42,209,000	280	54,083,000	236	47,451,000
Subtotal, research projects............	975	185,192,000	960	191,891,000	947	200,063,000
Research centers						
Core/specialized....	29	7,639,000	29	8,015,000	29	8,344,000
Other research						
Research career prog.	16	1,318,000	20	1,717,000	20	1,765,000
Cooperative clin. res	150	22,492,000	157	23,330,000	157	24,370,000
Biomedical research support............						
Minority biomedical support............		287,000		338,000		364,000
Other res. related...	21	1,243,000	26	1,567,000	26	1,611,000
Subtotal, other res.	187	25,340,000	203	26,952,000	203	28,110,000
Total, research grants	1,191	218,171,000	1,192	226,858,000	1,179	236,517,000

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Training:						
Individual awards						
Noncompeting........	64	1,723,000	57	1,551,000	69	2,037,000
Competing...........	38	958,000	38	1,089,000	26	696,000
Subtotal, individual awards...........	102	2,681,000	95	2,640,000	95	2,733,000
Institutional awards						
Noncompeting........	129	3,121,000	150	4,033,000	160	3,726,000
Competing...........	49	1,424,000	16	621,000	6	1,039,000
Subtotal, institutional awards.............	178	4,545,000	166	4,654,000	166	4,765,000
Total, training......	280	7,226,000	261	7,294,000	261	7,498,000
Research & development contracts...........	13	5,043,000	25	7,390,000	25	7,597,000
	FTEs		FTEs		FTEs	
Intramural research.	202	27,987,000	186	29,139,000	180	29,135,000
Research management and support.............	70	11,207,000	71	11,198,000	69	11,275,000
Extramural construction						
TOTAL................	272	269,634,000	257	281,879,000	249	292,022,000
Clinical trials		(24,368,000)		(25,319,000)		(26,357,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH
National Eye Institute

Summary of Changes

1994	Estimated budget authority	$281,879,000
1995	Estimated budget authority	292,022,000
	Net change	+10,143,000

	1994 Current Estimate Base		Change from Base	
	Pos. (FTE)	Budget Authority	Pos. (FTE)	Budget Authority
Changes:				
A. **Built-in:**				
1. Intramural				
a. Within grade increase..		$12,468,000		+$164,000
b. One less day of pay.....		12,468,000		-48,000
c. Annualization of January 1994 locality pay.....		12,468,000		+76,000
d. FY 1995 pay increases...		12,468,000		+153,000
e. FECF Unemp. Comp........		12,468,000		+8,000
f. Payment for Mgmt Fund		7,689,000		+316,000
g. Service and supply fund increase..............		1,266,799		+291,000
h. FTS increase............		8,962,000		+3,000
Subtotal...............				+963,000
2. Research Management & Support:				
a. Within grade increase....		4,539,000		+62,000
b. One less day of pay......		4,539,000		-18,000
c. Annualization of January 1994 locality pay.......		4,539,000		+27,000
d. FY 1995 pay increases....		4,539,000		+56,000

	1994 Current Estimate Base		Change from Base	
	Pos. (FTE)	Budget Authority	Pos. (FTE)	Budget Authority
e. FECF Unemp. Comp.......		4,539,000		+2,000
f. Payment for Mgmt Fund..................		2,234,000		+92,000
g. Service and Supply fund		4,425,000		+218,000
h. DHHS Working Capital Fund..................		316,000		+2,000
i. FTS increase...........		4,425,000		+1,000
Subtotal...............				+442,000
B. Program:				
1. Research projects grants:	No.	Amount	No.	Amount
a. Noncompeting............	680	137,808,000	+31	+14,804,000
b. Competeting..............	282	54,083,000	-44	-6,632,000
Total.................	960	191,891,000	-13	+8,172,000
2. Center grants	29	8,015,000	0	+329,000
3. Other research..........	203	26,952,000	0	+1,158,000
4. Training................	261	7,294,000	0	+204,000
5. Research and development contracts..............	25	7,390,000	0	+207,000
		FTEs	FTEs	
6. Intramural research.....	172	29,139,000	-1	-967,000
7. Research management and support................	69	11,198,000		-365,000
Subtotal...............			-1	+8,738,000
Total changes...........				+10,143,000

NATIONAL INSTITUTES OF HEALTH
National Eye Institute

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment........	257	249	-8
Full-time equivalent of overtime and holiday hours......	1	1	--
Average ES salary.....	$110,530	$112,860	+$2,330
Average GM/GS grade...	10.30	10.30	--
Average GM/GS salary	$45,000	$45,000	--
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)......	70,100	71,300	+1,200
Average salary of ungraded positions	25,900	23,700	-2,200
Personnel compensation:			
Permanent positions	$8,626,000	$8,702,000	+$76,000
Positions other than permanent..........	3,723,000	3,756,000	+33,000
Other personnel compensation.......	435,000	438,000	+3,000
Special personnel services...........	1,423,000	1,436,000	+13,000
Total personnel compensation.......	14,207,000	14,332,000	+125,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Personnel benefits....	2,571,000	2,593,000	+22,000
Benefits for former personnel...........	11,000	11,000	--
Travel and transportation of persons.............	426,000	438,000	+12,000
Transportation of things..............	75,000	75,000	--
Communications, and miscellaneous charges.............	414,000	410,000	-4,000
Printing and reproduction........	210,000	208,000	-2,000
Other Services:			
Consultant services.	246,000	244,000	-2,000
Other Services......	3,464,000	3,413,000	-51,000
Purchase from Govt. Accts...............	13,405,000	13,828,000	+423,000
Operation of GOCOs..	38,000	38,000	--
R&D Contracts.......	7,390,000	7,597,000	+207,000
Supplies and materials..........	3,429,000	3,402,000	-27,000
Equipment.............	1,841,000	1,418,000	-423,000
Grants, subsidies and contributions.......	234,152,000	244,015,000	+9,863,000
Total, budget authority..........	281,879,000	292,022,000	+10,143,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NEI

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	8,626	8,626	8,702	76
11.3	Other than full-time permanent	3,723	3,723	3,756	33
11.5	Other personnel compensation	435	435	438	3
11.8	Special personnel services payments	1,423	1,423	1,436	13
11.9	Subtotal, personnel compensation	14,207	14,207	14,332	125
12.1	Civilian personnel benefits	2,571	2,571	2,593	22
13.0	Benefits for former personnel	11	11	11	0
	Subtotal Pay Costs	16,789	16,789	16,936	147
21.0	Travel and transportation of persons	426	426	438	12
22.0	Transportation of things	75	75	75	0
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	414	414	410	(4)
24.0	Printing and reproduction	210	210	208	(2)
25.0	Other Services	16,953	15,815	16,185	370
26.0	Supplies and materials	3,429	3,429	3,402	(27)
	Subtotal non-pay costs	21,507	20,369	20,718	349
	Total Administrative Costs	38,296	37,158	37,654	496

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1994 House Report	Action Taken or to be Taken
Diabetic Retinopathy	
1. The House in its report 103-156, page 63, stated "The Committee urges NEI to continue to emphasize funding diabetic eye research to work toward eliminating the disproportionate ill effects of diabetes on minority groups. The Committee also encourages the Institute to consider expanding clinical and health services research on eye care and diabetes, including new authorities recently enacted."	1. Research on diabetic retinopathy continues to be a high priority to NEI. The most promising opportunities for research in this area are addressed in Vision Research - A National Plan: 1994-1998. This document, developed by the National Advisory Eye Council as part of NEI's formal program planning process, defines the scope and impact of important research areas of vision research, updates program goals and objectives, reviews current research support and scientific advances, and determines the key research questions to be addressed in FY 1994-1998. In addition, the NEI and the Juvenile Diabetes Foundation are partners in a cooperative program that will expand cell and molecular biology research on diabetic retinopathy.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1994 House Report	Action Taken or to be Taken
National Eye Health Education Program (NEHEP)	
2. The House in its report 103-156, page 63, stated "The Committee urges the National Eye Health Education Program (NEHEP) to include Spanish language and other culturally sensitive literature in its program and asks that particular emphasis be placed on reaching out to these minority groups, and the physicians who treat these groups, to ensure they receive proper eye health care and education."	2. The National Eye Health Education Program will conduct a variety of activities in FY 1994 to support the development of a culturally sensitive diabetic eye disease education program targeted to Hispanics with diabetes. Specific activities include establishing an ad hoc working group on Hispanic Outreach, representing a variety of health professionals, educators, and community leaders in the Hispanic community; conducting focus groups and in-depth interviews with the Hispanic community; and developing a communication plan to include the development and evaluation of appropriate education strategies and culturally sensitive health education materials.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1994 Senate Report	Action Taken or to be Taken
Glaucoma	
1. The Senate in its report 103-143, page 98, stated "The leading cause of blindness is glaucoma. Presently, no cure exists for glaucoma, but the scientific and technological capabilities now exist to make substantial progress against glaucoma through accelerated basic research, and research to determine why the rate of glaucoma is higher and the disease possibly more severe in African-Americans. The Committee urges the Institute to increase efforts in this important area."	1. The NEI has funded three new clinical trials in glaucoma, and a significant number of African-Americans will be recruited to participate. The Collaborative Initial Glaucoma Treatment Study will compare the efficacy of a medical regimen to filtration surgery as the initial treatment of newly-diagnosed primary open-angle glaucoma. The Ocular Hypertension Treatment Study will determine whether medical reduction of intraocular pressure prevents or delays the onset of glaucomatous optic nerve and/or visual field damage in ocular hypertensive subjects. The Early Manifest Glaucoma Trial is designed to determine whether and to what extent reduction of intraocular pressure influences the course of chronic open angle glaucoma. Participants will be randomized either to pressure lowering treatment or to observation without treatment.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Significant Items in House and Senate Appropriations Committee Reports

1994 Senate Report	Action Taken or to be Taken
Diabetic Retinopathy	
2. The Senate in its report 103-143, page 98, stated "The Committee urges NEI to continue to emphasize funding diabetic eye research to work toward eliminating the disproportionate ill effects of diabetes on minority groups. The Committee also encourages the Institute to consider expanding clinical and health services research on eye care and diabetes."	2. Research on diabetic retinopathy continues to be a high priority to NEI. The most promising opportunities for research in this area are addressed in Vision Research - A National Plan: 1994-1998. This document, developed by the National Advisory Eye Council as part of NEI's formal program planning process, defines the scope and impact of important research areas of vision research, updates program goals and objectives, reviews current research support and scientific advances, and determines the key research questions to be addressed in FY 1994-1998. In addition, the NEI and the Juvenile Diabetes Foundation are partners in a cooperative program that will expand cell and molecular biology research on diabetic retinopathy.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Authorizing Legislation

	PHS Act/Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Estimate	1995 Amount Authorized	1995 Budget Request
Research and Investigation..	Section 301	42§241	Indefinite	$274,585,000	Indefinite	$284,524,000
National Eye Institute......	Section 455	42§851	Indefinite		Indefinite	
National Research Service Awards.	Section 487(d)	42§288	$400,000,000	7,294,000	Such sums as necessary	7,498,000
Total, Budget Authority......				281,879,000		292,022,000

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation [1]
1985	$157,873,000	$272,097,000 [2]	$187,181,000	$178,591,000
1986	183,341,000	188,988,000 [3]	184,036,000	195,094,000
1986 Sequester				-8,389,000
1987 [4]	179,201,000	219,091,000	214,080,000	216,637,000
1988	184,829,000	234,382,000 [5]	231,529,000	224,947,000
1989	229,021,000 [6]	223,288,000 [7]	229,271,000	234,218,000
1990	223,777,000 [8]	240,636,000	241,774,000	239,889,000 [9]
1990 Sequester				-3,356,000
1991	247,392,000	254,887,000 [10]	258,324,000	253,241,000 [11]
1991 Sequester				-3,000
1992	272,260,000	272,260,000	267,229,000	269,300,000 [12]
1993	285,133,000	279,102,000	279,102,000	276,188,000 [13]
1994	272,201,000	290,260,000	290,260,000	290,260,000
1995	292,022,000 [14]			

[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Excludes $3,900,000 in NRSA training programs not considered.

[3] Excludes $5,231,000 in NRSA training programs not considered.

[4] The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH. The Senate Allowance and the appropriation spread the funding among the Institutes, including $104,000 for the NEI.

[5] Does not include funding for AIDS research consolidated at the Secretary's level.

[6] The 1989 request excludes funds for AIDS research and education ($4,947,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

[7] Excludes $5,620,000 in NRSA training programs not considered.

[8] The 1990 request excludes funds for AIDS research and education ($5,697,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

[9] Excludes enacted administrative reductions of $1,316,000.

[10] Excludes $7,105,000 in NRSA training programs not considered.

[11] Excludes enacted administrative reductions of $6,918,000.

[12] Reflects enacted administrative reductions totaling $1,702,000.

[13] Reflects enacted administrative reductions totaling $2,914,000.

[14] Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
EXTRAMURAL RESEARCH												
Vision research......	---	$212,417	---	$224,508	---	$229,891	---	$241,542	---	$251,612	---	$10,070
Intramural research...	170	25,606	200	28,512	202	27,987	186	29,139	175	29,135	-11	$ - 4
Research management and support..........	66	9,651	66	10,844	70	11,207	71	11,198	74	11,275	3	$ 77
Total obligations.....	236	247,674	266	263,864	272	269,085	257	281,879	249	292,022	-8	10,143
Unobligated balance lapsing..............		+91		+212		+549		---		---		---
Total, budget authority........	236	247,765	266	264,076	272	269,634	257	281,879	249	292,022	-8	10,143

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Eye Institute

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
272	$269,634,000	257	$281,879,000	249	$292,022,000	-8	+$10,143,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Eye Institute. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

Thousands of Americans are blinded each year by eye diseases and disorders of vision. An estimated 1.7 million people will have some degree of visual impairment in FY 1995 as a result of age-related macular degeneration alone, and approximately 100,000 will experience a devastating, rapid loss of vision. Although vision research has yielded effective treatments, nearly 24,000 diabetics are blinded each year due to diabetic retinopathy. Cataract accounts for over 6.3 million physician visits each year, with 29 percent of individuals aged 65-74 years having lens opacities that cause a decrease in vision. An estimated 3 million people have glaucoma, and 120,000 are blind as a consequence. These diseases account for a significant portion of the estimated $22.3 billion in direct costs and $16.1 billion in indirect costs that visual disorders and disabilities impose on our society each year.

Important progress has been made in a number of areas of vision research that are directed toward the prevention of disease or the prevention of the visual disability. Shown below are highlights of a few of the advances and opportunities in vision research:

- Diabetic Retinopathy. The enzyme aldose reductase (AR) may be a common link in many of the complications of diabetes, such as cataract, retinopathy, and damage to the kidneys, nerves, and blood vessels. Side effects associated with the use of the current generation of AR inhibitors limit their clinical application; opportunities exist for developing better drugs and other approaches to control AR activity, thus preventing the complications of diabetes.

- Retinitis Pigmentosa (RP). Molecular genetic technology has allowed the determination of the precise gene defects responsible for some forms of RP. Opportunities for early diagnosis, genetic counseling, and clinical therapeutics, such as gene therapy approaches, aimed at prevention of these blinding inherited diseases are well within reach.

- Age-Related Cataract. Research opportunities are being explored, based on recent findings indicating that α -crystallin, a structural protein in the lens of the eye, may play an important role in preventing cataracts.

- Glaucoma. Scientists have localized the gene for juvenile onset glaucoma, a form of the disease characterized by early adulthood onset and elevated intraocular pressure (IOP), to chromosome 1 and are now trying to isolate and characterize the gene. Additional research of this type may allow identification of the gene(s) for primary open angle glaucoma, the most prevalent form of the disease.

- Diabetic Eye Health Education. The NEI will modestly expand its highly successful eye health education activities to include Hispanic and Native Americans. The program will stress early detection and timely treatment of diabetic eye disease in preventing blindness and will encourage comprehensive eye examinations through dilated pupils.

The President's appropriation request of $292,022,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Eye Institute during the last five years has been as follows:

	Amount	FTE
FY 1990	$230,958,000	217
FY 1991	247,765,000	236
FY 1992	264,076,000	266
FY 1993	269,634,000	272
FY 1994	281,879,000	257

Purpose and Method of Operation

The National Eye Institute (NEI) is the principal component of the NIH responsible for conducting and supporting both nationally and internationally basic and clinical research, research training, health information dissemination, and other research oriented programs relative to blinding eye diseases, visual disorders, mechanisms of normal visual function, preservation of sight, and the special health problems and requirements of individuals who are visually-impaired or blind. Additionally, the NEI maintains an active intramural research program conducted by an internationally recognized team of scientists at its laboratory and clinical facilities located on the NIH campus in Bethesda, Maryland. In an effort to facilitate vision research and to establish clearly defined goals and objectives, the institute and the National Advisory Eye Council, in conjunction with the vision research community, have developed a series of long-range plans. The most recent of these, Vision Research--A National Plan: 1994-1998, was released in FY 1993 and will guide the NEI's research activities over the next five years.

Overall Budget Policy

The NEI FY 1995 budget request is $292,022,000, an increase of $10,143,000 or 3.6 percent compared to the FY 1994 level. At the request level, the Institute will support 711 noncompeting research project grants at $151,154,000 and 236 new and competing renewal grants at $47,451,000, compared to 680 and 280, respectively in FY 1994. A total of 29 centers will be supported in FY 1995 at $8,344,000. The other research grants category will be supported in FY 1995 at $28,110,000 for 203 awards. This request also includes $29,135,000 for intramural research and $11,275,000 for research management and support. With respect to total FTEs, the FY 1995 request of 249 FTEs represents a decrease of 8, compared to 1994.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

National Eye Institute

EXTRAMURAL RESEARCH

Authorizing Legislation - Sections 301, 455 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$228,652,000	$241,542,000	$251,612,000	+$10,070,000

VISION RESEARCH:

Research activities supported by the extramural vision research program address the leading causes of blindness and impaired vision in the U.S., including retinal diseases, corneal diseases, cataract, glaucoma, strabismus, and amblyopia. The program seeks to increase understanding of the normal development and function of the visual system; to understand the causes of, and better diagnose, prevent, and treat sight-threatening conditions; and, to enhance the rehabilitation, training, and quality of life of individuals who are partially-sighted or blind.

Funding for the Vision Research program during the last five years has been as follows:

	Amount
FY 1990	$197,820,000
FY 1991	212,482,000
FY 1992	224,548,000
FY 1993	228,652,000
FY 1994	241,542,000

Rationale for the Budget Request

The FY 1995 budget request for the extramural Vision Research program is $251,612,000, a $10,070,000 or 4.2 percent increase over the FY 1994 appropriation. With the requested funding, the NEI will build on the research foundation established in retinal and corneal diseases; cataract and glaucoma research; and strabismus, amblyopia, and visual processing research. The anticipated research will be conducted primarily using research grants, core awards (Specialized/Comprehensive Center awards), cooperative clinical trials, and research training awards. Provided below is a discussion of each of the research areas to be explored within the Vision Research activity.

Retinal Diseases

The retina, a delicate, light-sensitive tissue at the back of the eye, initiates the process of vision and transmits visual messages to the brain via the optic nerve. Diseases and disorders of the retina, collectively, are the leading cause of blindness in the United States.

Retinal Degeneration and Programmed Cell Death (Apoptosis). Apoptosis, or programmed cell death, seems to be an important mechanism used by the retina during its development and may play a role in retinal degeneration. Mutations in several retina-specific genes have been shown to cause photoreceptor degeneration in humans and mice. Although the mechanism by which these gene mutations lead to photoreceptor degeneration is unknown, NEI-supported research has suggested that there is a common pathway in the disease process. Apoptosis appears to play a role in all of these retinal degenerations through fragmentation of the DNA by intracellular enzymes at specific sites in the genome. If this is the case then there is the exciting possibility of an intervention for a variety of retinal degenerations based on inhibition of these DNA-cutting enzymes.

Molecular Genetics of Macular Degeneration. Macular degeneration is the most common cause of severe visual impairment in older persons in the United States. It robs otherwise healthy older Americans of useful vision, depriving them of the ability to read, drive, and enjoy leisure activities. There is no effective treatment for the vast majority of individuals with this condition because the basis for the disease is not understood. The genes for at least three forms of macular degeneration have been localized to specific chromosomes by NEI-sponsored investigators. A juvenile form of macular degeneration known as Best's disease has been mapped to chromosome 11. Two other forms of hereditary macular disease have been linked to chromosome 6. Additional molecular genetic research offers the opportunity to characterize the genes responsible for these macular degenerations, as well as the more prevalent age-related macular degeneration.

Retinitis Pigmentosa. Retinitis pigmentosa (RP) is a group of hereditary retinal degenerative diseases with an incidence of about 1 in 3,500 births in the United States. The emotional and economic costs of the disease to society are enormous, particularly since no effective treatments are known for most types of retinal degeneration. Results from a prospective, double-masked clinical trial designed to assess the effectiveness of vitamin A and/or E supplements in halting or slowing the progression of RP showed that adults who supplemented their diets with 15,000 IU of vitamin A daily had on average about a 20% slower annual decline of remaining retinal function than those not taking this dose.

NEI-supported research has led to significant advances in identifying the molecular defects in several different forms of RP. Scientists have found mutations in the light-sensitive photoreceptor pigment, rhodopsin, in some forms of the disease. Researchers have also found mutations in the gene for a key enzyme in the pathway that converts light to neural signals. In an uncommon form of retinal degeneration clinically related to RP, a mutation has been found in the gene for another photoreceptor protein, peripherin, which is thought to aid in stability of the photoreceptors. The identification of genetic defects in retinal degenerations is an important step in developing effective therapeutic strategies. With this information in hand, scientists are now able to explore the molecular mechanisms responsible for these diseases and to begin to translate this information into effective treatment and prevention strategies.

Corneal Diseases

Diseases and injury to the cornea are the leading cause of visits to clinicians for eye care in the United States and rank among the most painful of eye conditions. NEI-supported research on corneal diseases includes studies of ocular infections and inflammation, problems with tears and the ocular surface, refractive errors, corneal transplantation, and corneal wound healing.

Molecular Basis of Transparency. The structural framework of the cornea, the stroma, is unique among the connective tissues composed of the protein collagen, because it is transparent. Understanding the molecular basis of transparency requires a detailed knowledge of the regulation of the collagen types, as well as other proteins found in this tissue. Researchers supported by the NEI have cloned and sequenced the two genes for the major type of collagen in the cornea. Further study revealed the surprising observation that one of the genes is expressed in the lens as well as in the cornea. The second gene is located in the region of the gene for dysgenetic lens, a hereditary disorder involving the lens and the cornea that results in corneal opacity. Transgenic mice have now been prepared that carry defects in both genes. This research forms the groundwork for a more detailed examination of the unexpected role of this type of collagen in the embryonic development of the cornea and lens.

Herpes Simplex. About a half-million Americans are affected by ocular herpes, which often begins as a relatively painful sore on the surface of the cornea. The Herpetic Eye Disease Study in part examined the effect of steroid eye drops as a treatment for active herpetic stromal keratitis, an advanced infection that can lead to severe corneal scarring, inflammation of the interior of the eye, and even blindness. Researchers conducting the study reported rapid improvement of stromal keratitis with immediate steroid therapy, but for those patients having their first episode of stromal keratitis, topical steroids could be safely deferred. Long term follow-up of the patients continues.

Cataract

Cataract, a clouding of the lens of the eye that interferes with vision, is the leading cause of blindness worldwide. In the United States, cataract is responsible for more than 3.3 million cases of visual impairment and accounts for 1.5 million surgical procedures for extraction annually. Cataract surgery is the most frequent operation among older Americans. Reimbursement for cataract surgery (more than $5 billion in total) now accounts for approximately 12 percent of the entire Medicare Part B budget. The enormous burden of cataract will worsen in coming decades as the American population ages. The major goals of this program, therefore, are to determine the causes and mechanisms of cataract formation, to search for ways to slow or prevent the progression of cataract, and to develop and evaluate new diagnostic and therapeutic techniques in cataract management.

Lens Development and Models of Cataract Formation. Proper development of the eye is dependent on numerous interactions between embryonic tissues. Because lens formation is one of the earliest events in ocular development, it plays a critical role in the development of other eye tissues. Likewise, lens development is influenced by chemical signals it receives from other embryonic tissue that direct the processes of cell division and differentiation. NEI-supported scientists have identified a number of small chemical molecules, known as growth factors, that may be involved in these processes in the lens.

Overproduction of two of these growth factors in the lenses of transgenic mice lead to congenital cataracts. This demonstrates the importance of these molecules in lens development and has provided scientists with a new model for cataract formation.

Glaucoma

Glaucoma is a group of eye disorders which damage the optic nerve leading to blindness. Glaucoma is a major public health problem and the number one cause of blindness in African Americans. Approximately 3 million Americans have glaucoma, and as many as 120,000 are now blind from this disease. Blindness from glaucoma is estimated to cost the United States in excess of $1.5 billion annually in Social Security benefits, lost tax revenues, and health care expenditures. NEI extramural program activities in glaucoma are directed toward understanding the mechanisms of the disease through basic research, identifying risk factors, and preventing blindness.

Molecular Genetics. Little is known about the underlying causes of glaucoma and the accompanying nerve degeneration that leads to loss of vision. Furthermore, the relative influence of genetic and environmental characteristics is poorly understood. Juvenile onset glaucoma is one form of the disease that is characterized by onset in early adulthood and elevated IOP. NEI-supported scientists have been studying affected families in Michigan, New England, and Iowa in an attempt to identify a "glaucoma" gene and ultimately to characterize the protein encoded by this gene. Recently, the disease-associated gene has been mapped to chromosome 1. Although the link between juvenile onset glaucoma and the more prevalent primary open angle glaucoma is unclear, finding the gene responsible for one form of glaucoma is a beginning in the quest for identification of at least one of this disease's causative factors.

Regulation of Fluid Pressure in the Eye. An important role of the aqueous humor, the clear fluid that nourishes the cornea and lens, is to maintain the proper pressure in the eye. It is the balance between the production (inflow) of aqueous humor and its outflow from the front of the eye that maintains the proper pressure. A major aim of current glaucoma research is to gain a better understanding of the mechanisms that regulate these two pathways. Our understanding of outflow biology has been enhanced by a recent discovery that some nitrogen compounds lower intraocular pressure. This finding adds important information to our understanding of outflow regulation and opens the door to the possibility of new therapeutic strategies.

Strabismus, Amblyopia, and Visual Processing

Developmental disorders such as strabismus (misalignment of the eyes) and amblyopia (commonly known as "lazy eye") affect 2-4% of the United States population. Correction of strabismus is one of the most frequently performed of all surgical operations (about 700,000 operations each year). Blindness from amblyopia is preventable if the condition is detected and treated early in life. In addition to research on strabismus and amblyopia, the program supports research on neuro-ophthalmological disorders, presbyopia (the inability of the lens to focus on near objects to "accommodate"--that occurs with aging), and refractive errors. This program also supports research on more effective means to improve the quality of life of persons with visual impairments by helping them maximize their use of remaining vision or devising aids to assist those without useful vision. Three million Americans now have chronic visual conditions that are not correctable by eye glasses or contact lenses and that impair everyday function. About 900,000 Americans are legally blind, and approximately 100,000 are totally blind or have only the ability to perceive light but not formed images. Understanding visual processing and its disorders requires new knowledge of the visual nervous system, including the molecular, genetic, chemical, cellular, and integrative processes that underlie perception and the control of eye movements.

Development of Visual Pathways. In the visual system, a precise pattern of connections exists between the retina and the visual centers of the brain. This pattern is established during embryonic development and refined during early life. Scientists have shown that specific chemical signals are needed at the right time and the right place to establish a precise map, which is the basis for normal vision. Determining the nature of these signals may lead to the development of treatments to repair developmental abnormalities or areas damaged by injury.

Development of Myopia. More than 25% of the adult population of the United States is nearsighted (myopic). Myopia usually develops between the ages of six and 14 years. Recent experiments in animals have shown that a biological feedback mechanism controls the shape of the eyeball, and thus its optical properties. Scientists have found that the presence of visual images on the retina produces a signal within the eye which, through a cascade of events, can ultimately affect the structure and shape of the eye. These studies not only have improved our understanding of the causes of myopia, they also suggest that eventually we may be able to prevent it.

Optic Neuritis. Optic neuritis, an acute debilitating inflammation of the optic nerve that primarily affects women between the ages of 18 and 45, and is frequently the initial manifestation of multiple sclerosis (MS). The scientists conducting the Optic Neuritis Treatment Trial (ONTT) reported that a three-day, high-dose treatment with intravenous corticosteroids followed by a short course of oral corticosteroid reduced the rate at which study participants developed MS. The ONTT scientists had reported previously that their treatment enabled patients to recover their vision about two weeks sooner than would be the case without treatment. Long-term follow up of the patients continues.

National Eye Institute

INTRAMURAL RESEARCH

Authorizing Legislation - Sections 301, 455 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
202	$29,609,000	186	$29,139,000	180	$29,135,000	-6	-$ 4,000

The Division of Intramural Research of the NEI has developed a broad multidisciplinary research effort relating to blinding and disabling disorders of vision that integrates laboratory and clinical research in such areas as ocular inflammatory diseases, retinopathy, developmental and degenerative disorders of vision, cataract, and the effects of neurological defects on vision. The Division of Biometry and Epidemiology is also included in this budget activity.

Funding for the Intramural Research program during the last five years has been as follows:

	Amount	FTE
FY 1990	$23,615,000	154
FY 1991	25,632,000	170
FY 1992	28,530,000	200
FY 1993	29,609,000	202
FY 1994	29,139,000	186

Rationale for the Budget Request

The FY 1995 budget request for intramural research is $29,135,000, a $4,000 decrease from the FY 1994 level. The request represents the net effect of administrative cost and FTE decreases, and increases for mandatory central services requirements and pay raises. Within the amount requested, research priorities will include gene therapy research and cell and molecular biology.

Molecular Mechanisms of Ocular Disorders. Investigators have continued to study a broad range of topics relating to the biology of various tissues, looking in depth at the molecular mechanisms responsible for certain ocular disorders. The major emphases continue to be cataract and the ocular complications of diabetes. Investigators have found that the amino acid histidine at position 110 on the aldose reductase molecule (which has been shown to play a role in the ocular complications of diabetes) is critical for the molecule to function properly. Scientists are doing genetic mapping studies on a variety of genetic disorders that have ocular manifestations, including Usher's syndrome type I. These scientists have mapped two studies on a variety of genetic disorders that have ocular manifestations, including Usher's syndrome type I. These scientists have mapped two independent genes for Usher's syndrome type I to different locations on chromosome 11.

Visual Control of Eye Movement. Research efforts continue in the understanding of the systems within the brain that process visual information and produce eye movements, as well as understanding what happens when disease or trauma lead these systems to fail. Through the use of a superb animal model, researchers have found that the animals respond to simulations of motion projected on a screen with postural changes similar to those reported in humans. This will allow them to investigate further the regions of the brain that are known to process this type of visual motion information and to see whether alterations of these regions affect posture. Investigators were also able to locate the approximate region of the frontal eye fields in humans and alter certain eye movements after first locating this region in monkeys. By using information obtained from animal models to locate areas in the human brain that perform similar functions, we may gain a better understanding of how the intricate mechanisms that guide the visual process operate normally and how they might be impaired by disease or injury.

Ocular Complications of Diabetes. Researchers continue to concentrate on the development of new ophthalmic drugs, especially inhibitors of aldose reductase (AR)--an enzyme that has been linked to ocular and neural complications of diabetes. More effective and less toxic AR inhibitors that are unrelated to previous inhibitors have been developed using biochemical, pharmacological, and computer molecular design techniques. Scientists have continued to evaluate a galactose-fed dog model of diabetic retinopathy as it progresses to the sight-impairing proliferative stage. This dog model is the first experimental model that demonstrates both the clinical and histological changes found in all stages of diabetic retinopathy, making it particularly valuable in evaluating new treatments of this disease in the future.

Molecular Biology of the Eye. Research activities include studies of the lens, cornea, and retina and have also been directed toward the role of growth factors in eye development. Because the lens crystallins are multifunctional proteins that are expressed outside the lens and eye, research has increased during the last few years to include new areas of metabolism and gene expression in various tissues. In studies of the regulatory elements required for expression of genes in the eye and other tissues, scientists found that these elements are quite diverse with each having its own special properties. The elements may also be functionally redundant, that is, removing one does not necessarily eliminate the expression of the gene. A more complete understanding of gene expression in the eye may one day allow treatments to be directed to specific eye tissues.

Ocular Genetic Diseases and Gene Therapy. Research activities are directed toward gene expression and molecular interactions important to the eye, with the application of clinically relevant research findings for the prevention, diagnosis, and treatment of diseases affecting the eye and visual system. Scientists have continued their leadership role in the study of gyrate atrophy. Dietary intervention studies are continuing in families with two affected children. These studies have demonstrated a marked decrease in the retinal progression of this disorder in the children who began the dietary intervention at an early age. It is anticipated that this original work will lead to gene therapy aimed at preventing this disease. Additionally, scientists are working in conjunction with other NEI-supported scientists to develop objective and subjective methods of monitoring and documenting opacities in the lens. Monitoring and documenting human cataract development is a crucial step toward the ultimate testing of several medications that might be helpful in preventing or reversing human cataracts.

Retina-Specific Genes. Research is focused on elucidating new genes and biochemical mechanisms and learning the underlying causes of ocular diseases. Information derived from this research should allow intervention in the disease process before substantial damage to vision has been done or to apply rational methods of gene therapy before the terminal stages of the disease have been reached. Investigators have identified several genes that are predominantly or exclusively expressed in ocular tissues. These genes, as well as retina-specific genes, are being pinpointed to determine whether they are linked to eye diseases. An understanding of the normal complement of genes and their functions in these tissues is the first step in being able to control or reverse hereditary disease processes that involve these tissues, such as retinitis pigmentosa and retinoblastoma.

Ocular Inflammatory Diseases. Basic and clinical research is conducted related to the evaluation, diagnosis, and treatment of ocular inflammatory diseases. Clinical scientists continue to provide major support and have a major commitment to studies of the ocular complications of AIDS. Additionally, scientists have continued their study of toxoplasmosis, a protozoan infection that can have devastating ocular consequences. They have developed a reliable ocular model for this disease in which characteristic damage to the brain and retina can be demonstrated. This model is being used to evaluate the virulence of various strains of disease.

Linxian Cataract Studies. Within NEI's intramural biometry and epidemiology activities, cataract studies were conducted that investigated the effect of vitamin/mineral supplements on the risk of developing age-related cataracts. Specifically, two trials were conducted in China, in conjunction with two National Cancer Institute trials using the same vitamin/mineral interventions in a population with chronic nutritional problems and high rates of esophageal and stomach cancer. In these highly cost-effective studies of populations with chronic deficiencies of multiple nutrients, NEI investigators and their colleagues found that use of the supplements was associated with a decreased risk of nuclear cataract. Additional research is underway to determine whether these findings apply to less nutritionally deficient populations.

The Eye Disease Case-Control Study. In a large epidemiologic study of neovascular age-related macular degeneration, scientists have also found an increased risk of disease was associated with cigarette smoking and higher levels of serum cholesterol. Decreased risk was associated with postmenopausal use of estrogens and higher serum levels of carotenoids. Results from the study are consistent with an hypothesis linking risk factors for cardiovascular disease with age-related macular degeneration.

The hypothesis that higher serum levels of micronutrients with antioxidant capabilities may be associated with a decreased risk of age-related macular degeneration was evaluated in the study. Persons with higher levels of carotenoids and those with higher levels of an antioxidant index derived from serum measurements of Vitamin C, Vitamin E, carotenoids and selenium also showed a decreased risk of macular degeneration. Results from this observational study are now being tested in a clinical trial.

National Eye Institute

RESEARCH MANAGEMENT AND SUPPORT

Authorizing Legislation - Sections 301, 455 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
70	$11,373,000	71	$11,198,000	69	$11,275,000	-2	+$ 77,000

This budget activity provides resources for crosscutting Institute administrative management as well as programmatic functions including the Office of the Director (OD), the Division of Extramural Activities, Division of Basic Vision Research, Division of Collaborative Clinical Research, the Office of International Program Activities, the Office of Administrative Management, and the Office of Science Policy and Legislation, in which the National Eye Health Education Program (NEHEP) is organizationally located. The OD is the focal point for decision making regarding the overall scientific direction of the NEI. The Associate Director for Extramural Research is responsible for administrative management of extramural basic and clinical research, training, and collaborative activities. NEHEP, the first federally sponsored nationwide eye health education program, works in partnership with over 50 public and private organizations. The initial focus is on public and professional education programs for glaucoma and diabetic eye disease. If Americans at risk for developing these diseases were regularly screened and treated to preserve their sight, the Federal government would be able to save over $1.5 billion annually spent on blindness related costs. The cost of blindness includes Social Security benefits, lost income tax revenues, and health care expenditures.

In addition, this budget activity includes support for the National Advisory Eye Council. Together, these Research Management Support components ensure effective and efficient management of extramural and intramural programs, both nationally and internationally facilitate cooperative academia-industry-government technology transfer, and outreach.

Funding for Research Management and Support during the last five years has been as follows:

	Amount	FTE
FY 1990	$9,523,000	63
FY 1991	9,651,000	66
FY 1992	10,998,000	66
FY 1993	11,373,000	70
FY 1994	11,198,000	71

Rationale for the Budget Request

The FY 1995 request for research management and support is $11,275,000, a $77,000 increase or .1 percent increase over FY 1994. The RMS activity provides for the Institute's overall scientific and management direction. This includes program development and analysis, evaluation of the extent of eye diseases, and the management and allocation of resources. Also included in this activity is the programmatic and fiscal management of approximately 1,500 research grants and contracts, annually, by NEI's Extramural Research staff. They are responsible for developing program plans, communicating scientific priorities to the scientific community, evaluating ongoing scientific progress supported by various extramural research mechanisms, and managing the allocation and spending of funds for grants and contracts.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director.......	42	42	41
Intramural Research Program..	202	186	180
Extramural Vision Research...	28	29	28
Total, NEI.................	272	257	249

Average GS/GM Grade	
1990	10.37
1991	10.50
1992	10.50
1993	10.45
1994	10.30
1995	10.30

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

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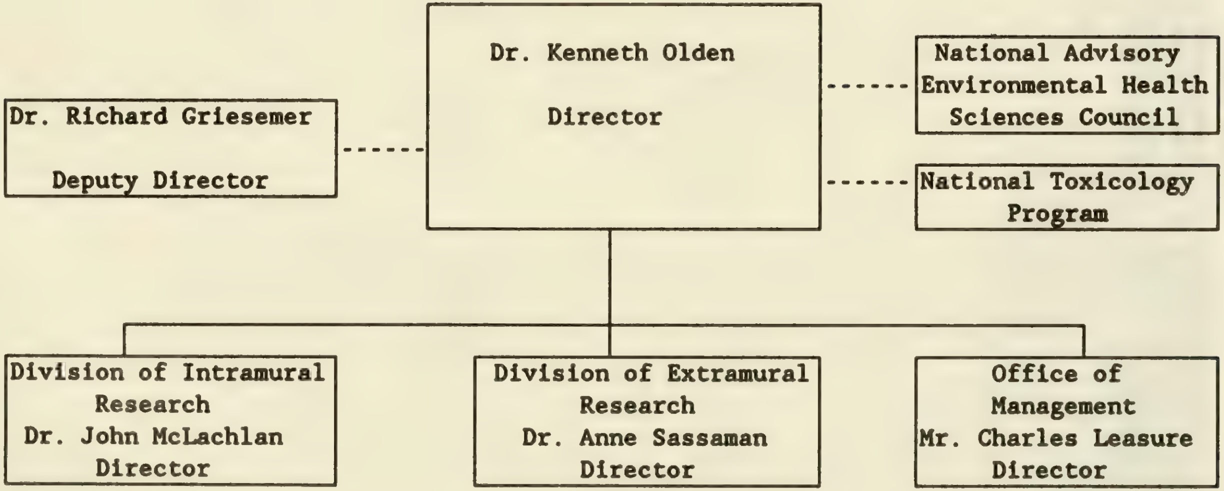
NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out Section 301 and 311 and title IV of the Public Health Service Act with respect to environmental health sciences, [$264,249,000] *$267,955,000 of which $2,867,000 shall not become available for obligation until September 19, 1995.* (Department of Health and Human Services Appropriation Act, 1994.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Language Analysis

Language Provision	Explanation
"...of which $2,867,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$255,115,000	$264,249,000	$267,955,000
Section 216 reduction	-1,861,000		
Section 511 reduction	-2,041,000		
Section 513 reduction	-26,000	---	---
Subtotal, adjusted appropriation	251,187,000	264,249,000	267,955,000
Comparable transfer to the Office of AIDS Research for HIV Activities	-4,272,000	-5,608,000	
Subtotal, adjusted budget authority	246,915,000	258,641,000	267,955,000
Unobligated balance, lapsing	-132,000	---	---
Total, obligations	246,783,000	258,641,000	267,955,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1993 - $75,554,000; 1994 - $79,927,000; 1995 - $79,927,000. Excludes $17,352 for Royalties in FY 1993 and $12,000 anticipated for Royalties in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Mechanism

Research Grants	1993 Actual No.	1993 Actual Amount	1994 Appropriation No.	1994 Appropriation Amount	1995 Estimate No.	1995 Estimate Amount
Research Projects:						
Noncompeting	283	$58,820,000	300	$67,996,000	307	$68,244,000
Administrative supplementals	(9)	1,128,000	(10)	503,000	(10)	523,000
Competing:						
Renewal	44	10,637,000	49	10,388,000	54	11,959,000
New	67	13,077,000	73	15,097,000	81	17,397,000
Supplementals	1	27,000		--		--
Subtotal, competing	112	23,741,000	122	25,485,000	135	29,356,000
Subtotal, research projects	395	83,689,000	422	93,984,000	442	98,123,000
Research Centers	18	17,167,000	20	19,616,000	22	22,064,000
Other Research:						
Research career programs	25	2,346,000	26	2,446,000	26	2,514,000
Minority biomed. res. support	--	460,000	--	462,000	--	480,000
Other research related	9	812,000	25	1,456,000	25	1,497,000
Subtotal, other research	34	3,618,000	51	4,364,000	51	4,491,000
Total, Research Grants	447	104,474,000	493	117,964,000	515	124,678,000
Training						
Individual awards:						
Noncompeting	25	653,000	36	965,000	38	1,029,000
Competing:						
New	20	560,000	11	289,000	9	243,000
Supplementals		30,000				
Subtotal, individ	45	1,243,000	47	1,254,000	47	1,272,000

Institutional awards:						
Noncompeting	265	5,588,000	385	8,968,000	398	9,319,000
Competing:						
Renewal	94	2,543,000	20	506,000	11	273,000
New	8	198,000	4	104,000	--	--
Supplementals	48	1,247,000	--	--	--	--
Subtotal, inst	415	9,576,000	409	9,578,000	409	9,592,000
Total, training	460	10,819,000	456	10,832,000	456	10,864,000
Research & Development Contracts	108	50,126,000	107	49,776,000	109	51,998,000
	FTEs		FTEs		FTEs	
Intramural Research	653	72,333,000	631	70,630,000	613	70,999,000
Research Management and Support	97	9,163,000	104	9,439,000	102	9,416,000
Total, NIEHS	750	246,915,000	735	258,641,000	715	267,955,000
Clinical Trials		(--)		(2,000,000)		(2,500,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Summary of Changes

1994 Estimated budget authority	$258,641,000
1995 Estimated budget authority	267,955,000
Net change	+9,314,000

	1994 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increases		$34,477,000		+$468,000
b. One less day of pay		34,477,000		-132,000
c. Annualization of January 1994 locality pay increases		34,477,000		+274,000
d. January 1995 pay increases		34,477,000		+448,000
e. Increase in unemployment compensation		180,000		+27,000
f. Increased cost of centrally furnished services		1,662,000		+68,000
g. Increased cost of FTS				+9,000
h. Increased cost of Service and Supply Fund		1,946,000		+70,000
i. Increased cost of laboratory supplies, materials, and other expenses		34,491,000		+905,000
Total				+2,137,000
2. Research management and support:				
a. Within grade increases		5,461,000		+74,000
b. One less day of pay		5,461,000		-21,000
c. Annualization of January 1994 locality pay raise		5,461,000		+53,000
d. January 1995 pay raise		5,461,000		+71,000
e. Increased cost of centrally furnished services		789,000		+33,000
f. Increased cost of FTS				+1,000
g. Increased cost of Service and Supply Fund		88,000		+25,000
h. Increased cost of laboratory supplies, materials, and other expenses		3,189,000		+68,000
i. DHHS Working Capital Fund		331,000		+2,000
Total				+306,000
Subtotal				+2,443,000

Summary of Changes--continued

	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	300	68,499,000	+7	+268,000
b. Competing	122	25,485,000	+13	+3,871,000
Total	422	93,984,000	+20	+4,139,000
2. Research centers	20	19,616,000	+2	+2,448,000
3. Other research	51	4,364,000	--	+127,000
4. Research training	456	10,832,000	--	+32,000
5. Research and development contracts	107	49,776,000	+2	+2,222,000
Subtotal, extramural		178,572,000		8,968,000
		(FTEs)		(FTEs)
6. Intramural research	631	70,630,000	-18	-1,768,000
7. Research management and support	104	9,439,000	-2	-329,000
Subtotal, program				+6,871,000
Total changes				+9,314,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment...............	735	715	-20
Full-time equivalent of overtime and holiday hours.........	5	5	---
Average ES salary....................	$110,522	$112,290	+1,768
Average GM/GS grade..................	10.35	10.35	---
Average GM/GS salary	44,317	45,026	+709
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)..................	69,247	70,355	+1,108
Average salary of ungraded positions.	30,170	30,652	+482
Personnel compensation:			
Full-time permanent	$24,226,000	$24,643,000	+$417,000
Other than full-time permanent.....	6,191,000	5,694,000	-497,000
Other personnel compensation.......	669,000	674,000	+5,000
Special personnel service payments.	2,429,000	2,445,000	+16,000
Total personnel compensation....	33,515,000	33,456,000	-59,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Personnel benefits	6,398,000	6,397,000	-1,000
Benefits for former personnel.....	25,000	25,000	---
Travel and transportation of persons....................	1,000,000	1,045,000	+45,000
Transportation of things..........	152,000	152,000	---
Rent, communications, and utilities..................	6,018,000	6,018,000	---
Printing and reproduction.........	571,000	581,000	+10,000
Other services:			
Consulting services.............	226,000	241,000	+15,000
Other..........................	13,729,000	13,970,000	+241,000
Purchases from Govt. Accts......	5,829,000	5,829,000	---
R&D contracts..................	49,776,000	51,998,000	+2,222,000
Supplies and materials............	7,873,000	7,893,000	+20,000
Equipment.........................	4,733,000	4,808,000	+75,000
Grants, subsidies & contributions.	128,796,000	135,542,000	+6,746,000
Interest.........................	---	---	---
Total budget authority by object................	258,641,000	267,955,000	+9,314,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIEHS

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	24,226	24,226	24,643	417
11.3	Other than full-time permanent	6,191	6,191	5,694	(497)
11.5	Other personnel compensation	669	669	674	5
11.8	Special personnel services payments	2,429	2,429	2,445	16
11.9	Subtotal, personnel compensation	33,515	33,515	33,456	(59)
12.1	Civilian personnel benefits	6,398	6,398	6,397	(1)
13.0	Benefits for former personnel	25	25	25	0
	Subtotal Pay Costs	39,938	39,938	39,878	(60)
21.0	Travel and transportation of persons	1,000	1,000	1,045	45
22.0	Transportation of things	152	152	152	0
23.2	Rental payments to others	590	590	590	0
23.3	Communications, utilities, and miscellaneous charges	5,045	5,045	5,045	0
24.0	Printing and reproduction	571	571	581	10
25.0	Other Services	17,350	18,566	18,822	256
26.0	Supplies and materials	7,873	7,873	7,893	20
	Subtotal non-pay costs	32,581	33,797	34,128	331
	Total Administrative Costs	72,519	73,735	74,006	271

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Significant Items in House, Senate and Conference Appropriations Committee Reports

1994 House Report	Action Taken or to be Taken
Breast Cancer	
1. The House in its report 103-156, page 63, stated, "The Committee encourages NIEHS to continue its research in under-standing how manmade and natural substances in the environment may act as hormones and cause certain diseases such as breast cancer."	1. NIEHS recently sponsored a meeting in Washington, D.C. entitled Estrogens in the Environment III: Global Health Implications that addressed a variety of topics such as basic cell and molecular biological research on estrogens; effects of estrogenic chemicals on fetal development; studies of non-traditional sites of estrogen action such as brain and sperm; some of the ubiquitous sources of estrogen in the environment; and the health implications of estrogens in humans and wildlife. Some of the potential health outcomes considered were breast cancer, endometriosis, and reproductive disorders in human males.
Toxicology Program	
2. The House in its report 103-156, page 63, stated, "The Committee is concerned with the reduced number or mixture of substances being tested through the National Toxicology Program (NTP) over the past years. The NTP has a proven track record in the identification of chemicals or substances which are most likely to cause a carcinogenic hazard to humans. The Committee urges that, at a minimum, 15 new studies of chemicals or substances, or combination or mixture of substances, be started in 1994 for identifying potential carcinogenicity using the current standard protocol NTP experimental design."	2. Prior to chemicals being studied for carcinogenicity, it is essential that a complete toxicological characterization of the chemical be completed to determine a number of potential health effects, including carcinogenicity. Currently, at least 15 new substances will undergo complete toxicological evaluations during 1994. In addition to chronic and carcinogenicity studies, NTP is expanding its mechanistic research to better understand the molecular and cellular basis for toxicity.

Significant Items, Continued

Environmental Chemical Agents	Action Taken or to be Taken
3. The House in its report 103-156, page 63 and 64, stated, "The Committee encourages NIEHS to consider continuing support of ongoing efforts to assess and interpret data related to the biological and clinical effects of chemical and physical agents in the environment."	3. NIEHS scientists are placing increased emphasis on quantitative and computational biology, specifically in the areas of risk assessment and mathematical/ molecular modeling. The Institute has recently entered into an agreement with the Environmental Protection Agency and continues an agreement with the Agency for Toxic Substances and Disease Registry to collaborate on the development of methodology for quantitative risk assessment. Furthermore, the Institute has contracted for clinical research centers that provide access to clinical populations and facilities for NIEHS investigators, allowing them to extend findings from basic laboratory research into an appropriate clinical setting and to evaluate more fully the clinical effects of chemical and physical agents in the environment.
Dioxins 4. The House in its report 103-156, page 64, stated, "The Committee remains supportive of continued research in the area of the impact of dioxins on human health."	4. Research into sensitive molecular markers of biochemical effects of dioxins is expanding and we are using these markers to determine relative sensitivities of rodents and humans and to establish the link between dioxin-mediated changes in gene expression and toxic effects. In addition, we are directing an international effort which is attempting to identify the basis for the inter-individual variation in human responses to dioxin. Finally, we are using our dosimetry and mechanism data to develop biologically-based mathematical models for dioxin's cancer and noncancer effects.

1994 Senate Report

Rural Health	Action Taken or to be Taken
1. The Senate in its report 103-143, page 99, stated, "The Committee understands NIEHS will continue its research into health effects of agricultural exposures, including occupational exposures and exposures through ground water contamination."	1. Over the past two years NIEHS has supported two environmental health sciences (EHS) centers committed to the investigation of the health effects of agricultural chemicals. A recent requirement by the Institute, that the EHS centers have outreach programs to educate and provide assistance to persons potentially exposed to environmental agents through occupational or other methods, has provided direct application of research information to the affected population.
Toxicology Program	
2. The Senate in its report 103-143, page 100, stated, "The Committee commends the Institute for making a conscious effort to evaluate alternative animal model systems and to compare their predictive value against current rodent testing protocols and urges the Institute to maintain a vigorous program in the development of alternative models."	2. The transgenic mouse model is a powerful new tool for testing potential human carcinogens. Transgenic models also show considerable promise for improving our understanding of mechanisms of toxicity and carcinogenicity. The carcinogenesis models contain mutated positive oncogenes or deleted tumor suppressor genes, such as the p53 tumor suppressor gene knockout model. These models may provide new sensitive systems that could reduce the number of animals required in each test and allow extensive studies of more compounds. Transgenic-p53 knockout mice which lack the p53 tumor suppressor gene are potentially the most valuable mouse lines generated to date as a carcinogen detection system. Experiments underway will determine the pattern of tumor induction in comparison to the same chemicals in the standard mouse used for the NTP bioassay.

Significant Items, Continued

3. The Senate in its report 103-143, page 101, stated, "The Committee urges additional resources be focused on validating nonmammalian methods. The Committee recognizes that such methods cannot only be more humane, but are essential to meet the demand for quicker, cheaper, more reliable testing of potentially hazardous substances."	3. Two small fish species, medaka and guppy, are being evaluated for their usefulness in predicting chemical carcinogenicity. This is a 5-year effort that will test three compounds known to cause cancer in rodents. Potential advantages of fish as a bioassay test system include lower costs, more rapid results, and the ability to evaluate chemical mixtures and chemicals found in water. Transgenic fish that may be useful in detecting and studying the mutagenic effects of xenobiotics are being developed by NIEHS intramural scientists. These fish have the potential to serve as models to detect the specific tissues that may be affected by cancer-causing agents and may be useful as environmental sentinels to detect the presence of such agents in water sources. The frog embryo teratogenesis assay (FETAX) is currently being validated as a developmental toxicity screening assay to detect toxicants that may cause birth defects. This system uses a laboratory-adapted frog species and offers the potential advantages of cost effectiveness, rapid results, and a high predictive accuracy for mammalian developmental toxicants. The NIEHS marine and freshwater biomedical science centers program provides core resource support for the use of nonmammalian aquatic/marine organisms to study various human environmental health problems. The program has been very productive scientifically, with important discoveries about the mechanisms by which chemicals cause various toxic effects, such as cancer, birth defects, reproductive failure, and many others.

Neurobehavioral and Environmental Neurotoxicology Research	Action Taken or to be Taken
4. The Senate in its report 103-143, page 100, stated, "The Committee notes that previous instructions to NIEHS have focused on expanding research on noncancer health effects and toxicants. A 1990 Office of Technology Assessment report on "Neurotoxicity" concluded that neurotoxic substances pose a substantial threat to public health and that Federal research programs were not adequately addressing neurotoxicity concerns. The Committee reemphasizes its support for an increase in intramural research on neurobehavioral and environmental toxicology research. The Committee is concerned by the continued lack of representation from the behavioral science community on the National Advisory Environmental Health Science Council. Such expertise would enhance the effort to incorporate neurobehavioral neurotoxicology research in NIEHS' intramural program and its applied disease prevention research efforts."	4. Scientists in NIEHS' Division of Intramural Research are engaged in a number of neurotoxicology research projects, including studies on developmental neurotoxicology of pesticides; development and validation of a neurobehavioral test battery in animal toxicity studies; environmental factors and Alzheimer's disease; lead and other neurotoxins as risk factors for amyotrophic lateral sclerosis; studies on chemical exposures and neuronal and glial cell injury in critical areas of the brain; and studies on the interrelationships between the nervous, immune and endocrine systems. As required by its charter, NIEHS' National Advisory Council does have a representative from the behavioral sciences community. Furthermore, scientific presentations have been made to the Council by members of the behavioral sciences community.

Significant Items, Continued

Native American Initiative	Action Taken or to be Taken
5. The Senate in its report 103-143, page 100, stated, "The Committee recommends that the NIEHS collaborate with the National Tribal Environmental Council to conduct a national tribal environmental health study with member tribes to build a national data center which would be required to respond to the environmental health research needs of tribes. The Committee recommends NIEHS initiate a study aimed at collecting biological, epidemiological, and ecological data on the environmental health conditions of native American communities."	5. NIEHS scientists and grant-supported scientists are currently conducting studies on the health effects of: consuming mercury contaminated fish in a Native American population which will characterize body burdens of methylmercury including transport to the brain; the association between consuming fish and game contaminated with PCBs from a Superfund site with neurocognitive delays in children exposed to breast milk by a Native American population in upstate New York; and mercury-containing amalgams used in dental care of Native American children on reservations. The NIEHS Director and selected staff will attend the National Tribal Environmental Council meeting in April 1994. The meeting will be held in Albuquerque, New Mexico and will address environmental concerns on Native American reservations.
Environmental Health Sciences Research Centers	
6. The Senate in its report 103-143, page 100, stated, "The 18 NIEHS supported environmental health sciences research centers are critical to the mission of the overall Institute, and the Committee continues to strongly support the centers program to ensure that NIEHS has the means to respond to the growing needs in environmental health sciences research."	6. Executive leadership of the Institute believes in the need for additional centers to support the many emerging problems confronting the environmental sciences. To this end, the Institute has received a number of new applications for centers and plans to issue one or two additional awards in the near future. This competitive approach for the support of centers ensures that current grantees remain on the cutting edge of research and positions the Institute to do the highest quality research in support of the many environmental health problems facing our nation.

Significant Items, Continued

	Action Taken or to be Taken
7. The Senate in its report 103-143, page 100, stated, "The Committee has learned that funding for the NIEHS centers program has declined in constant dollars over the last several years. The committee requests a report from the Institute regarding funding declines and reasons for the declines in time for next year's hearings."	7. The overall appropriation for the NIEHS has declined in constant dollars over the past several years due in part to the Nation's economic status in a given budget year and in part to the Institute's competitive status among the other NIH components. Since investigator-initiated research project grants are the major priority at NIH, other mechanisms of support, including research center grants, may not always receive the desired funding levels. However, in each year since fiscal year 1990, when the NIH Cost Management Plan was implemented, EHS centers have been funded at or slightly above the prior year's total cost.
Health Effects of Radiation	
8. The Senate in its report 103-156, page 100 and 101, stated, "The Committee recognizes the significant short and long-term benefits of research on the health effects of radiation. The unfortunate incident at Chernobyl offers a tremendous opportunity to understand the impact of chronic radiation exposure. Therefore, the Committee urges the National Institute of Environmental Health Sciences to take the lead and focus greater attention on research in this area, including the conducting of such studies in the affected new independent states and other countries as appropriate. Such activities should be coordinated with the Centers for Disease Control and Prevention and other relevant agencies and departments and should support the private sector initia-tive of the International Consortium for Research on the Health Effect of Radiation. The Committee recognizes the desirability of additional resources to be devoted to this important area."	8. The radiation release from Chernobyl offers a unique opportunity to track human health effects of these exposures. Cancer is one obvious disease that needs to be examined. The National Cancer Institute has an ongoing program that will answer questions of cancer-related effects arising from the exposures to high levels of radiation released at Chernobyl. Cancer, however, is only one of many important possible health outcomes from these exposures. Birth defects, miscarriages, infertility, and immune system disorders are also possible consequences of exposures to radiation released from Chernobyl. NIEHS is collaborating with concerned citizens, academic researchers, and other Federal agencies to identify research gaps and to arrange further studies to ascertain the incidence of these effects from radiation.

Significant Items, Continued

1994 Conference Report

Breast Cancer	Action Taken or to be Taken
1. The Conference in its report 103-275, page 23, stated, "The Conferees direct the National Cancer Institute and the National Institute of Environmental Health Sciences to become more aggressive in the pursuit of research into the role environmental factors play in contributing to elevated rates of breast cancer such as have been observed in Nassau and Suffolk counties, in the State of New York, and in other counties throughout the United States."	1. NIEHS' Division of Intramural Research is conducting several different research activities related to human breast cancer. As for most human diseases, breast cancer is the result of a complex interaction between genetic and environmental factors and current research projects are focused on both etiologic aspects. It has recently been shown that a class of ubiquitous environmental toxicants may be related to breast cancer etiology. Many organochlorine compounds, for example, PCB, DDT, DDE, and dioxin, are known to possess estrogenic or antiestrogenic potential, and the total body levels of several of these compounds have been shown to correlate directly with increased breast cancer risk. Since attributable risk factors account for only a small percentage of breast cancer risk, it is imperative that studies to investigate such relationships be extended. Institute scientists are conducting a number of studies to identify further such chemicals, to elucidate their genetic/molecular mechanisms of action, and to determine their potential role in the etiology of various diseases such as breast cancer.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation.........	Section 301 and 311	42§241	Indefinite	$247,809,000	Indefinite	$257,091,000
National Institute of Environmental Health Sciences..............	Section 463	42§285	Indefinite		Indefinite	
National Research Service Awards........	Section 487(d)	42§288	$400,000,000	10,832,000	Such sums as necessary	10,864,000
Total Budget Authority				258,641,000		267,955,000

NATIONAL INSTITUTES OF HEALTH

National Institutes of Environmental Health Sciences

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation1/
1986	$183,755,000	$188,319,000 2/	$198,319,000	$ 197,478,000
1986 Sequester				-8,492,000
1987	187,995,000	209,872,000	208,067,000	209,294,000
1988	198,431,000	225,724,000 3/	220,709,000	215,666,000
1989	218,471,000 4/	216,985,000 5/	223,168,000	223,454,000 6/
1990	226,471,000 7/	232,479,000	234,048,000	232,476,000 8/
1990 Sequester				-3,242,000
1991	235,792,000	244,832,000 9/	242,765,000	241,028,000 10/
1992	254,484,000	254,912,000	250,873,000	251,575,000 11/
1993	261,513,000	252,564,000	255,115,000	251,187,000 12/
1994	261,306,000	264,249,000	264,249,000	264,249,000
1995	267,955,000 13/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes $8,502,000 in NRSA training programs not considered.

3/ The House allowance consolidated AIDS funding ($4,091,000) in the Office of Assistant Secretary for Health.

4/ The 1989 request excludes funding for AIDS research and education ($4,234,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes $9,183,000 in NRSA training programs not considered.

6/ Excludes $2,714,000 administrative reduction.

7/ The 1990 request excludes funds for the National HIV program ($4,377,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

8/ Excludes $788,000 enacted administrative reduction.

9/ Excludes $10,586,000 in NRSA training programs not considered.

10/ Excludes enacted administrative reduction of $8,064,000.

11/ Excludes enacted administrative reduction of $4,871,000 and enacted rescission of $456,000. Includes $3,000,000 real transfer from the National Cancer Institute.

12/ Excludes enacted administrative reduction of $3,928,000.

13/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Biological response to environ agents...		$65,217		$73,215		$75,154		$82,736		$86,323		+$3,587
Applied toxicological res. and testing		56,156		55,045		53,336		54,861		57,355		+2,494
Biometry and risk estimation..........		11,635		11,584		8,943		10,527		10,934		+407
Resource and manpower development...		27,578		27,840		27,986		30,448		32,928		+2,480
Subtotal...		160,586		167,684		165,419		178,572		187,540		+8,968
Intramural research...	655	67,318	673	70,370	653	72,226	631	70,630	613	70,999	-18	+369
Research management and support.........	91	8,188	95	9,214	97	9,138	104	9,439	102	9,416	-2	-23
Total obligations.....	746	236,092	768	247,268	750	246,783	735	258,641	715	267,955	-20	+9,314
Unobligated balance lapsing............	--	27	--	82	--	132	--	--	--	--	--	--
Total Budget Authority..........	746	236,119	768	247,350	750	246,915	735	258,641	715	267,955	-20	+9,314

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute of Environmental Health Sciences

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
750	$246,915,000	735	$258,641,000	715	$267,955,000	-20	+$9,314,000

General Statement

From conception to death we are all exposed to a wide variety of environmental agents. These exposures are important because, in combination with our individual genetic susceptibility, they can contribute to our risks of developing numerous diseases and disorders. Diseases and dysfunctions with an environmental component include cancer, birth defects, infertility, neurological impairments, immune disorders, and lung dysfunctions. Because environmental exposures can be controlled or avoided, they represent one of the most promising means of improving our nation's health and reducing health care costs.

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental causes by understanding how environmental factors, individual genetic susceptibility, and age interrelate to affect our health. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. NIEHS supports its research efforts through investigator-initiated research grants and center grants at research institutions throughout the country, through competitive contracts with private sector R&D firms, and in its own intramural laboratories.

Environmental health research is at a critical and exciting juncture. New refinements in molecular biology techniques provide unprecedented opportunities to understand the molecular and cellular basis of environmentally-associated diseases. A detailed understanding of the molecular basis of environmentally-associated disorders will have a major impact on how we manage environmental health risks. Advances in this arena will lead to:

- novel molecular intervention strategies to circumvent effects of existing exposures;

- more confident use of animal data in predicting human health effects;

- reduction of use of animals in testing through development of innovative short-term assays and use of schemes that predict toxicity based on chemical structures; and

- more refined assessment of individual risks based on genetic susceptibilities to environmentally-associated diseases.

To ensure that it supports the most promising research areas, the NIEHS recently underwent an extensive planning exercise. Both the intramural and extramural communities were involved and consensus among the Institute's many research partners is being sought. The research priorities were structured around the core NIEHS responsibilities of providing the science needed for public health decisions, of translating this research into prevention and intervention strategies, and of communicating this information to the scientific and lay communities.

The NIEHS document, "Vision for the Future," highlights the need to focus on environmental components of human disease; the need to understand the basic biology of environmentally associated disorders; and the need to use this mechanistic understanding of environmentally caused effects in risk assessment schemes. This fundamental knowledge opens new opportunities for developing new molecular prevention and intervention schemes to circumvent adverse health effects of environmental exposures. The NIEHS vision also acknowledges the Institute's responsibility to provide the science base needed to guide policy in such areas as environmental equity, global climate change, and bioethics. Finally a communication strategy, which involves reaching out both to research partners and to the lay public, is envisioned as a cornerstone of the Institute's efforts to improve our nation's health through an awareness of the environmental components of diseases and dysfunctions.

The five year funding history for the NIEHS is:

	Amount	FTE
FY 1990	$224,449,000	716
FY 1991	236,119,000	746
FY 1992	247,350,000	768
FY 1993	246,915,000	750
FY 1994	258,641,000	735

Purpose and Method of Operation

The purpose of NIEHS' research is to provide a good understanding of how environmental factors, interacting with individual genetic susceptibilities over the course of a lifetime, can lead to diseases and disabilities. NIEHS and public policy agencies use this information to define public risks, to devise prevention and intervention strategies in the treatment of environmentally induced diseases, and to communicate the risks and risk-reduction techniques to the public.

The investigator-initiated research project grant program is the Institute's primary mechanism for supporting studies conducted by university scientists. These studies involve programs related to biological response to environmental agents, applied toxicological research and testing, and biometry and risk estimation. The scientists use all available tools of biomedical research, including basic biomedical studies, epidemiology, and toxicology. For the most part, this mechanism supports either a discrete, specified project by the named investigator or a broadly based, multidisciplinary program that includes several projects that have a specific major objective or basic theme.

Through grants to research centers it is possible to assemble a critical mass of scientific talent and apply it to the complex scientific questions which typify all environmental health problems. Supplemental funds are available to the centers for data collection and evaluation in the event of major accidents or disasters. In addition, the centers can support small pilot projects that enable a researcher to determine if a comprehensive research grant application is feasible.

Through the research career program, the Institute supports career development of researchers by issuing research career development awards, academic/teacher awards, clinical investigator awards, and physician-scientist awards. This mechanism also supports the Environmental/Occupational Medicine Academic awards. Other research grant awards support major conferences, small instrumentation, and scientific review and evaluation activities.

The National Research Service Award program supports research training of scientists for careers in basic and applied research into the human health implications of environmental exposures. The training is concentrated in the areas of toxicology, pathology, reproductive biology, mutagenesis, epidemiology and biostatistics, and molecular biology. Fellowship awards are made to individuals and training grants are made to institutions. The goal is to supply the critical scientific expertise necessary to solve environmental health problems encountered by individuals, patients, and the community in which they reside. It is also the goal of this program to reach out to underutilized populations, such as minorities and women, and encourage their participation as members of the environmental health sciences workforce.

The research and development contract mechanism is used to support specific research studies characterizing chemical toxicity and improving the testing methods used to determine toxicity and to support studies in basic and applied statistics, biomathematics, epidemiology, molecular modeling, and risk assessment.

The intramural research activity is made up of three major scientific programs plus associated technical and administrative support. The Environmental Toxicology Program is the lead program for NTP responsibilities; it plans and directs toxicology and carcinogenesis studies that characterize the toxicity of environmental agents. The Environmental Carcinogenesis Program studies the pathological, cellular, and molecular basis of cancer in humans and experimental animals and the effects of environmental agents on these processes. The Environmental Biometry and Epidemiology Program conducts basic research in statistics, epidemiology, and biomathematics related to the assessment of risk from exposure to environmental agents.

The research management and support activity provides salary and other support for the Office of the Institute Director, the Division of Extramural Research and Training, and portions of the Office of Management.

Overall Budget Policy

The FY 1995 budget request for NIEHS is $267,955,000, an increase of $9,314,000 over the FY 1994 estimate. Seventy percent of the budget request would support research grants, training, and contract activities, and 30 percent of the request would support intramural research and research management activities.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

In FY 1995, the budget request would fund 135 competing grants at an average cost of $217,500. The anticipated success rate in the budget request is 22.0 percent. The FY 1995 budget request would support 307 noncompeting research project grants at an average cost of $222,300.

Seventeen environmental health sciences centers and five marine and freshwater biomedical sciences centers would receive $22,064,000 in support from this request. Other research grants would receive $4,491,000.

The FY 1995 request would support 456 research trainees at an estimated cost of $10,864,000.

Contracts to support research and development in toxicity testing and test development, in risk estimation methods, and for other scientific problems in environmental health are projected at $51,998,000. Approximately 109 contracts would be supported.

Intramural research funds of $70,999,000 and 613 FTEs and research management and support funds of $9,416,000 and 102 FTEs are requested.

The FY 1994 administrative cost estimate will be changed to reflect a technical adjustment to include the NIH Management Fund costs. The FY 1994 current estimate is $74,953,000, an increase of $2,434,000 over the amount specified in the FY 1994 appropriation bill.

National Institute of Environmental Health Sciences

Extramural Research

Authorizing Legislation - Section 301 and 463 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$165,419,000	$178,572,000	$187,540,000	+$8,968,000

Institute-supported grantees and contractors contribute to the success of its mission through free-ranging and directed research in biological response to environmental agents, applied toxicological research and testing, and biometry and risk assessment. Also, NIEHS supports the development of key national resources in environmental public health and the training of environmental health scientists through three major grant programs: environmental health sciences core centers, marine and freshwater biomedical sciences centers, and National Research Service Award (NRSA) grants.

The five year funding history of this activity is:

	Amount
FY 1990	$152,328,000
FY 1991	160,588,000
FY 1992	167,705,000
FY 1993	165,419,000
FY 1994	178,572,000

Rationale for the Budget Request

The FY 1995 budget request for Extramural Research is $187,540,000, an increase of $8,968,000 over the FY 1994 estimate of $178,572,000. With the FY 1995 extramural request these funds will provide support for the following activities: biological response to environmental agents, $86,323,000, an increase of $3,587,000 or 4.3 percent over the FY 1994 estimate of $82,736,000; applied toxicological research and testing, $57,355,000, an increase of $2,494,000 or 4.5 percent over the FY 1994 estimate of $54,861,000; biometry and risk estimation, $10,934,000, an increase of $407,000 or 3.9 percent over the FY 1994 estimate of $10,527,000; and resource and manpower development, $32,928,000, an increase of $2,480,000 or 8.1 percent over the FY 1994 estimate of $30,448,000.

Good Science For Good Decisions: The NIEHS extramural research community collectively represents the greatest concentration of talent focused on environmental health concerns in this country. Their research efforts span the entire spectrum of human health concerns. This document highlights some of their accomplishments and plans in the areas of women's health and children's health.

Breast Cancer: Breast cancer continues to be a major health problem for women. The death rate increased by a disturbing 24% between 1979 and 1986. Today one in nine women will develop breast cancer. Recent research, sponsored by NIEHS and others, supports the probable role of environmental factors in the development of some breast cancers. This work showed an association between a woman's likelihood of developing breast cancer and her blood levels of DDE, a metabolite of the pesticide DDT. Emerging evidence is implicating other contaminants which, in common with DDE, have the ability to mimic the female hormone, estrogen, and consequently affect development of estrogen-dependent cancers. The NIEHS extramural community is: conducting surveys to assess the incidence of breast cancer in women exposed to environmental estrogens such as pesticides; examining the association of different monthly hormonal rhythms with breast cancer risks; identifying those environmental agents that have estrogenic and anti-estrogenic effects; and attempting to assess how the timing of critical exposures lead to increased susceptibility for breast cancer.

Endometriosis: An estimated 10% - 15% of the premenopausal female population suffer from endometriosis, a condition in which uterine tissue grows outside of the uterus. Endometriosis is the leading cause of pain and infertility in this population. At present the cause of this disease is unknown. Provocative findings were recently published by NIEHS grantees who found that 79% of the monkeys they exposed to the common contaminant, dioxin, suffered from high rates of endometriosis. This finding was unexpected, particularly since the highest daily dose was only 25 parts per trillion. This result suggests an important environmental component for developing endometriosis. It is important because dioxin exposures will become more widespread as hospitals, in response to the AIDS crisis, become increasingly dependent upon disposable supplies which, when incinerated, release dioxins into the atmosphere. The NIEHS is pursuing this line of investigation by testing for dioxin and other chlorinated compounds in women who suffer from endometriosis.

Osteoporosis: Osteoporosis is a debilitating condition found in one-third to one-half of all postmenopausal women. It is characterized by fragility of the bone with hip fractures being the most serious consequence. Each year 250,000 people are hospitalized with hip fractures and one-half of these people are unable to walk independently again. Consequences of osteoporosis cost society an estimated $7-10 billion annually. Cadmium, lead and possibly other heavy metals found in the environment may be significant factors in developing this disease. NIEHS-supported scientists are investigating the ability of environmental agents to contribute to bone loss and are determining the molecular mechanisms by which they exacerbate this bone loss. Understanding the molecular basis for environmentally associated bone loss will be pivotal in devising therapies to circumvent this effect.

Birth Defects/Learning Disabilities: The developing fetus and infant represent particularly vulnerable targets for environmental agents. An adverse effect sustained at this time can cause health problems throughout an individual's life. NIEHS-supported research has shown measurable declines in

IQ in children having relatively low levels of lead in their blood. The NIEHS and the NIH Office of Research on Minority Health are collaborating to fund clinical trials to evaluate the ability of a therapeutic agent, Succimer, to prevent learning and neurobehavioral disorders associated with low blood lead levels. In addition, NIEHS grantees are continuing to identify which ages are more vulnerable and whether there is recovery if exposure ceases.

Prevention/Intervention: Use of animal testing and epidemiologic studies to identify environmental hazards to human health will remain a cornerstone of the nation's prevention and intervention program. The NIEHS is seeking to enhance the effectiveness of hazard identification while at the same time reducing the number of laboratory animals needed for this testing. Additionally the NIEHS is attempting to develop a knowledge of the molecular mechanisms by which environmental agents affect our health. This mechanistic knowledge will form the basis for more reliable extrapolation of animal testing results to the human condition, thus reducing our need for further testing. Equally important, it can provide a basis for developing innovative molecular prevention and intervention strategies that can be used to circumvent the adverse effects of environmental exposures. Two examples are given to illustrate the usefulness of these initiatives.

Molecular Intervention - Environmentally Induced Liver Cancer: Chemical warfare is as old as life itself. Many plants produce toxins and, to combat the effects of consuming food contaminated with these toxins, people have developed detoxifying enzyme systems. Sometimes, though, these detoxifying enzymes are not sufficient when extremely high amounts of natural toxins are present in the food supply. Such is the case for a class of grain molds which, under certain environmental conditions, produce aflatoxins that infect grain and get into the food supply. Aflatoxin is implicated in the high incidences of liver cancer found in many developing countries which lack the ability to control its presence in the food supply. NIEHS-supported researchers are investigating the use of a metabolism modifier, Oltipraz, which can increase the rate at which people detoxify aflatoxin. If successful, this therapy holds great promise for application to other environmentally associated cancers through manipulation of natural detoxifying mechanisms found in the body.

Animal Alternatives - Sentinel Animals: Wildlife can serve both as sentinels for human risks from environmental exposures and as early indicators of compromised environmental quality. Recent observations of reduced fertility and increased androgyny among wild birds and amphibians have alerted biologists to the ability of environmental estrogens, such as DDT metabolites and polychlorinated biphenyls (PCBs), to adversely affect reproduction and sex characteristics. Reproductive endocrine effects of certain chemicals have been reported by a NIEHS-supported researcher. These toxic effects are very similar to those reported in several mammalian species which suggests their mechanisms of toxicity may be common to most, if not all, vertebrate species, including humans. A knowledge of endocrine lesions caused by reproductive toxicants may enable clinical tests to be developed for their detection in humans, and treatments to be designed to restore reproductive function. These examples show that an assessment of wildlife health can lead to critical clues for environmental components of human health.

Communication: The usefulness of NIEHS research findings can only be realized when shared with public policy makers, other governmental agencies, health professionals, and the American public. The NIEHS has long excelled at communicating information to the research and regulatory communities. Now the NIEHS is exploring ways to improve its outreach to lay communities.

Community Outreach: Environmental concerns tend to be localized. Farming communities in Iowa have different concerns than fishing communities in Maine. In order to extend its presence throughout the nation and to offer specialized services to such diverse populations, the NIEHS has called upon its Environmental Health Centers to develop community outreach programs. Community outreach is now considered a critical component of the Centers' performance and has been included as a measure of Center success.

Outreach to Underserved Populations: The burden of environmental exposures falls disproportionately on minority and other disadvantaged populations. These same populations tend to be underserved by the medical community and underrepresented in biomedical research studies. The NIEHS is examining ways in which to extend help and information to these groups through its Centers program. Currently the NIEHS funds fifteen Environmental Health Centers; this small number clearly hampers our ability to reach many needy populations. For these reasons the NIEHS has initiated a Developmental Center program to encourage universities to develop programs that address concerns of underserved populations. It is hoped that the guidance and experience these universities receive by participating in the Developmental Center program will enable them to successfully compete for Environmental Health Center grants in the future. The first of these Developmental Center grants was recently awarded to Tulane-Xavier Universities.

National Institute of Environmental Health Sciences

Intramural Research

Authorizing Legislation - Section 301 and 463 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
653	$72,333,000	631	$70,630,000	613	$70,999,000	-18	+$369,000

Institute scientists provide a critical link between basic and applied environmental research. The close proximity of individual laboratories offer many opportunities for sharing ideas and research findings. Thus, NIEHS intramural scientists involved in research on cellular and molecular processes can interact with intramural scientists doing applied research and, together, they can develop a more mechanistic understanding of environmental health problems.

The five year funding history of this activity is:

	Amount	FTE
FY 1990	$64,018,000	627
FY 1991	67,335,000	656
FY 1992	70,424,000	673
FY 1993	72,333,000	653
FY 1994	70,630,000	631

Rationale for the Budget Request

The FY 1995 budget request for Intramural Research is $70,999,000, an increase of $369,000 over the FY 1994 estimate of $70,630,000. The following are examples of efforts supported by this budget activity. The FY 1994 administrative cost estimate will be changed to reflect a technical adjustmnet to include the NIH Management Fund costs.

Good Science for Good Decisions: The NIEHS mission encompasses the full spectrum of diseases and disorders afflicting the human population. The discussion below highlights efforts focused on a subset of this population - women and children.

Breast and Ovarian Cancers: One in 200 American women have inherited a genetic defect that renders them more susceptible to developing breast and ovarian cancers. This susceptibility gene, BRCA1, is being mapped by NIEHS intramural scientists. Once the gene is identified, these scientists plan to use it to create special transgenic mice that will enable them to study in detail how this gene acts and how environmental agents can affect its functions.

Uterine Fibroids: The most common tumors in women are benign uterine fibroids. These tumors are present in 20% - 30% of all women over age 30. African-American women are the most susceptible group; 50% of African-American women are diagnosed with uterine fibroids compared to 20% of Caucasian-Americans. The major symptoms of this disease are pelvic pain, abnormal bleeding, and infertility. It is one of the major reasons for a woman having surgical removal of her uterus. Racial differences persist even in surgical outcomes - African-American women are three times more likely to die from complications from this surgery than are their Caucasian-American cohorts. There is a considerable body of evidence to support a role of estrogen in development of this tumor. The NIEHS has a long-standing interest in the subtle effects of environmental estrogens which could, in combination with endogenous estrogen, have an impact on development of this disease. The clear racial differences also indicate a need to understand how genetic susceptibilities, in combination with environmental exposures, affect disease development. The NIEHS is conducting studies to define the environmental and genetic underpinnings of uterine fibroid development. This information could lead to prevention programs which will dramatically decrease the incidence of what is a major health problem in the U.S.

Environmental Estrogens: The female hormone, estrogen, directs and controls cell growth and differentiation by binding to important estrogen receptor proteins located throughout the body. Many environmental compounds can bind to these same receptor proteins, thus acting as "environmental estrogens". Examples of environmental estrogens include many of the chlorinated pesticides such as DDT and kepone, polychlorinated biphenyls (PCBs), natural plant products in our diet, and the growth promoter used in cattle, diethylstilbestrol (DES). These environmental compounds, although weakly estrogenic, may play a role in diseases such as cancers of the breast, uterus, and ovaries, endometriosis, and uterine fibroids. NIEHS intramural scientists are exploring the basic biology of these environmental estrogens and attempting to define the role they play in these diseases.

Consequences of Fetal Exposure to Diethylstilbestrol: The developing embryo is a particularly vulnerable target. Many compounds to which a pregnant woman is exposed are able to cross the placenta and affect the rapidly dividing fetal cells. Effects of these exposures sometimes do not become apparent until adulthood. The NIEHS intramural program has been vigorously exploring this phenomenon through research on diethylstilbestrol (DES). This compound is a potent synthetic estrogen which, from the 1940's to the 1970's, was used to prevent miscarriages. Between 5 to 10 million people were exposed before it was banned for this use. People who were exposed to DES as fetuses develop many problems in adult life. The daughters are at increased risk of developing a rare vaginal cancer, clear cell adenocarcinoma; the sons are at increased risk of developing testicular cancer; and both sexes are more likely to experience reproductive problems. NIEHS intramural scientists are exploring the molecular basis of these effects. Additionally these scientists have conducted long-term, multigenerational animal studies which have indicated a need to monitor the third generation, or grandchildren, for possible effects arising from DES exposures to their parents during development. Results from these studies will also suggest avenues to explore the effects of more weakly estrogenic compounds such as the many chlorinated chemicals released into the environment.

Prevention/Intervention: Use of traditional animal testing and epidemiologic studies to identify environmental hazards to human health will remain a cornerstone of the nation's prevention and intervention program. The strength of these techniques will be greatly improved with incorporation of new insights into the molecular basis of toxic effects.

Novel Animal Assays - Functional Toxicology: Animal studies often provide only descriptive information, revealing the toxicity of an environmental agent by its ability to cause adverse effects such as tumors, histopathologic abnormalities, or genetic changes. Relatively large numbers of animals are required to assess these kinds of changes. NIEHS intramural scientists are exploring novel ways of coupling our developing knowledge of the molecular basis of toxicity with assays that could screen large numbers of chemicals for these effects. The initial "functional toxicology" assays will evaluate the ability of chemicals to interrupt cellular communication by binding to protein receptors critical to producing communication signals.

Improving Risk Assessment Models: The mathematical manipulations used to generate risk assessment values represent an area where NIEHS can make important contributions. Drawing upon its multidisciplinary intramural workforce, NIEHS is developing improved risk assessment models for use by regulatory agencies. Institute scientists are concentrating on ways in which an understanding of the molecular mechanisms of toxicity can be incorporated into risk assessment schemes. These efforts will greatly enhance the ability of regulators to relate environmentally induced changes in laboratory animals to expected outcomes in human populations. This type of precision is expected, ultimately, to reduce the need for multiple large animal studies to assess the toxicity of chemicals.

Communication: The usefulness of NIEHS research findings can only be realized when these findings are shared with public policy makers, other governmental agencies, health professionals, and the American public.

Environmental Health Perspectives: No scientific journal currently addresses the full spectrum of environmental health issues. To meet this need, the NIEHS has redesigned its journal, *Environmental Health Perspectives (EHP)*. In the future the journal will be published monthly and will contain a news section that will identify important and emerging issues across a broad spectrum of environmental health areas. It will be aimed at both the scientific and informed lay public and will provide a forum for commentary, discussion, and circulation of ideas. The remainder of the monthly journal will contain peer-reviewed scientific articles. The former *EHP* will be continued as a monograph series to report on scientific proceedings.

National Institute of Environmental Health Sciences

Research Management and Support

Authorizing Legislation - Section 301 and 463 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
97	$9,163,000	104	$9,439,000	102	$9,416,000	-2	-$23,000

This budget activity supports the staff and related expenses involved in the overall management of the Institute. Included are activities such as the Director's immediate office, individuals responsible for communications, the planning and evaluation function and the review and management of the Institute's grant and contract programs.

The five year funding history of this activity is:

	Amount	FTE
FY 1990	$8,103,000	89
FY 1991	8,196,000	91
FY 1992	9,221,000	95
FY 1993	9,163,000	97
FY 1994	9,439,000	104

Rationale for the Budget Request

The FY 1995 budget request for Research Management and Support is $9,416,000, a decrease of $23,000 below the FY 1994 estimate of $9,439,000. Research management and support funds several organizational units charged with carrying out Institute-wide responsibilities. These units are the Office of the Director, the Division of Extramural Research and Training, some portions of the Office of Management, and the Office of Communications. The FY 1994 administrative cost estimate will be changed to reflect a technical adjustment to include the NIH Management Fund costs.

Good Science for Good Decisions: Managerial support of the research programs conducted by NIEHS include the need to provide the infrastructure necessary for research in the technologically demanding field of environmental health sciences.

Envisioning the Future: Guiding the NIEHS into the 21st century requires that a common vision be shared by NIEHS and its many partners. For this reason NIEHS management has developed a strategic vision based on ideas solicited from its intramural and extramural communities. NIEHS sees its stakeholders as extending beyond its intramural and extramural scientists, however. Consequently the strategic vision is being used as a vehicle for soliciting ideas from the other stakeholders - professional organizations, industry groups, labor unions, and environmental advocacy groups.

Prevention/Intervention: NIEHS exists within a larger social framework. Responding to these responsibilities to the community, management is ensuring that NIEHS seek input into research needs for some of the social and political issues that revolve around public concerns for a safe environment.

Environmental Justice: Environmental justice is a newly emerging social issue. It refers to the fact that where one works and lives is largely dependent upon socioeconomic factors. Intuitively, one would expect that the poor and politically disenfranchised are at a greater risk of living near hazardous waste sites or working at hazardous occupations. For these reasons they would be more likely to suffer from environmentally related diseases than would those in the middle and upper socioeconomic classes. The NIEHS, in collaboration with the Environmental Protection Agency, the Centers for Disease Control and Prevention, and the Office of Research on Minority Health of the National Institutes of Health, is sponsoring a workshop to solicit ideas for research needs from environmental justice advocates and representatives of affected communities. This workshop will be held in February 1994.

Communication: The NIEHS has strong communication programs with the scientific community and federal regulators. Communication with other groups, however, is a need identified in its Strategic Vision document. Some of the attempts to reach to the lay public have been identified above. Of particular note is the outreach component now included as an Environmental Health Center responsibility and the newly revamped *Environmental Health Perspectives*. Other efforts are discussed below.

Partnerships - Non-federal: There are a vast number of private advocacy groups who have an interest in results of studies generated by the NIEHS/NTP. These groups include environmental advocacy groups, labor unions, industrial consortia, and animal welfare groups. The NIEHS is developing ongoing dialogues with these organizations in the hope that the unique expertise and perspectives of these individuals can lead to improvements in the design of toxicological studies.

Outreach: Two important groups - health care providers and citizens of environmentally affected communities - have traditionally been unaware of NIEHS-generated research and databases. The NIEHS is diligently investigating cost-effective, efficient mechanisms which would allow access by these critical users of environmental health information.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Appropriation	1995 Estimate
Office of the Director:			
Immediate Office	33	34	33
Office of Communications	7	7	7
Office of Occupational Health and Technical Services	25	24	24
Office of Program Planning and Evaluation	9	10	9
Office of Computer Technology and Services	10	10	10
Office of Institutional Development	5	5	4
Subtotal	89	90	87
Division of Intramural Research	478	464	451
Division of Extramural Research and Training	38	44	43
Office of Management:			
Immediate Office	4	4	4
Facilities Engineering Branch	60	57	55
Personnel Management Branch	17	15	15
Budget Management Branch	4	4	4
Administrative Services Branch	25	23	23
Contracts and Procurement Management Branch	35	34	33
Subtotal	145	137	134
Total, NIEHS	750	735	715

Average GS/GM Grade

1990	9.87
1991	10.01
1992	10.13
1993	10.30
1994	10.35
1995	10.35

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

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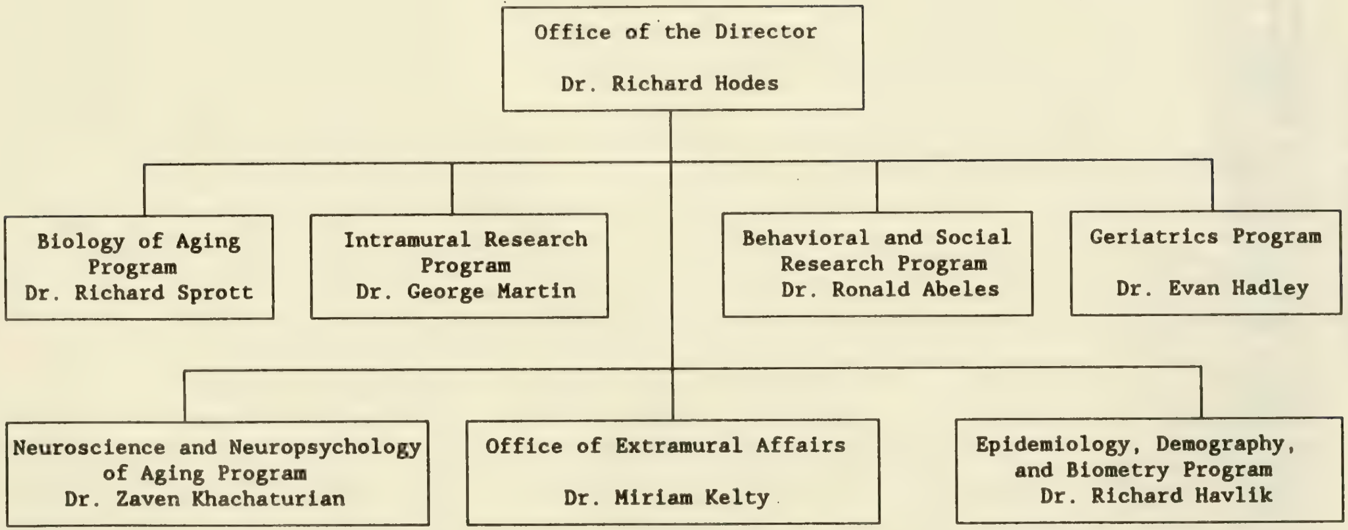
NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to aging, [$420,303,000] $433,701,000 *of which $4,559,000 shall not become available for obligation until September 19, 1995*. (Department of Health and Human Services Appropriation Act, 1994.)

National Institute on Aging

Language Analysis

Language Provision	Explanation
". . . of which $4,559,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation....................	$404,468,000	$420,303,000	$433,701,000
Section 511 0.8% reduction	-3,236,000		
Section 513 consultant services reduction............	-162,000		
Section 216 S&E reduction........	-1,146,000		
Subtotal, adjusted appropriation.............	399,924,000	420,303,000	433,701,000
Real transfer to other NIH accounts for Tuberculosis Research.......	-393,000	----	----
Comparative transfer to the Office of AIDS Research, NIH for HIV Activities.....................	-1,153,000	-1,664,000	----
Subtotal, adjusted budget authority...........	398,378,000	418,639,000	433,701,000
Unobligated balance lapsing.......	-8,000	----	----
Total, obligations...........	398,370,000	418,639,000	433,701,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1993 -- $3,960,000; 1994 -- $4,000,000; 1995 -- $4,000,000.

Note: Excludes $13,200 for Royalties received in FY 1993 and $21,500 in FY 1994.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants						
Research projects:						
Noncompeting	704	$193,518,000	683	$195,637,000	681	$196,116,000
Admin. suppl	(66)	2,381,000	(42)	2,220,000	(42)	2,309,000
Competing						
Renewal	58	15,225,000	87	26,241,000	98	33,196,000
New	123	24,699,000	150	31,217,000	166	33,543,000
Supplemental	25	4,646,000	7	1,355,000	8	1,456,000
Subtotal, competing	206	44,570,000	244	58,813,000	272	68,195,000
Subtotal, res. proj	910	240,469,000	927	256,670,000	953	266,620,000
Research Centers						
Spec./comp. ctrs	50	51,058,000	56	53,420,000	57	56,420,000
Other research						
Res. career program	110	8,917,000	124	10,200,000	124	10,547,000
Minority biom. res		928,000		882,000		907,000
Other res. related	39	2,767,000	57	3,015,000	61	3,364,000
Subtotal, other res	149	12,612,000	181	14,097,000	185	14,818,000
Total, research grants	1,109	304,139,000	1,164	324,187,000	1,195	337,858,000

Training						
Individual awards:						
Noncompeting	20	469,000	18	451,000	25	599,000
Competing	13	375,000	17	419,000	10	293,000
Subtotal, individual	33	844,000	35	870,000	35	892,000
Institutional awards:						
Noncompeting	350	8,947,000	315	8,968,000	319	9,421,000
Competing	73	1,836,000	84	2,372,000	80	2,239,000
Subtotal, institutional	423	10,783,000	399	11,340,000	399	11,660,000
Total, training	456	11,627,000	434	12,210,000	434	12,552,000
Research & development contracts	46	21,255,000	69	22,568,000	69	23,200,000
	FTEs		FTEs		FTEs	
Intramural Research	305	38,259,000	293	37,170,000	284	37,537,000
Research management and support	167	23,098,000	165	22,504,000	161	22,554,000
TOTAL	472	398,378,000	458	418,639,000	445	433,701,000
Clinical Trials	•	(15,708,000)		(14,283,000)		(13,557,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Summary of Changes

1994 Estimated budget authority	$418,639,000
1995 Estimated budget authority	433,701,000
Net change	+15,062,000

	1994 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
Changes:				
A **Built-in:**				
1. Intramural				
a. Within-in grade increases		$18,517,000		+$240,000
b. One less day of pay		18,517,000		-70,000
c. Annualization of January 1994 locality pay increase		18,517,000		+163,000
d. January 1995 pay raises		18,517,000		+225,000
e. Federal employees compensation fund, unemployment compensation		18,517,000		+15,000
f. Payment for centrally furnished services		4,433,000		+182,000
g. Increase for FTS		200,000		+4,000
h. Increase for service and supply fund		1,941,000		+77,000
i. Increased cost of laboratory materials & other supplies		14,220,000		+366,000
Subtotal				+1,202,000
2. Research Management & Support:				
a. Within-in grade increases		10,075,000		+143,000
b. One less day of pay		10,075,000		-39,000
c. Annualization of January 1994 locality pay increase		10,075,000		+93,000
d. January 1995 pay raises		10,075,000		+123,000
e. DHHS Working Capital Fund		353,000		+3,000

Summary of Changes--continued

	1994 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
f. Payment for centrally furnished services......		2,587,000		+106,000
g. Increase for FTS........		200,000		+2,000
h. Increase for service and supply fund.........		1,941,000		+43,000
i. Increased cost of laboratory materials & other supplies........		9,842,000		+254,000
Subtotal................				+728,000
	No.	Amount	No.	Amount
B Program:				
1. Research project grants:				
a. Noncompeting............	683	197,857,000	-2	+568,000
b. Competing..............	244	58,813,000	+28	+9,382,000
Subtotal.................	927	256,670,000	+26	+9,950,000
2. Research centers............	56	53,420,000	+1	+3,000,000
3. Other research..............	181	14,097,000	+4	+721,000
4. Training....................		12,210,000		+342,000
5. Contracts...................		22,568,000		+632,000
	FTEs		FTEs	
6. Intramural..................	293	37,170,000	-9	-835,000
7. Research Management and Support..............	165	22,504,000	-4	-678,000
Subtotal.............				+13,132,000
Total Changes.........				+15,062,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Full-time equivalent employment......	458	445	-13
Full-time equivalent of overtime and holiday hours..................	3	3	0
Average SES salary..................	$107,918	$107,918	--
Average GS grade....................	10.30	10.26	-0.04
Average GS salary...................	$37,231	$36,359	-$872
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207).	$82,006	$82,990	+$984
Average salary of ungraded positions.	$25,836	$26,146	+$310
Personnel compensation:			
Full-time Permanent................	$15,846,000	$15,977,000	+$131,000
Other than full-time permanent......	5,243,000	4,884,000	-359,000
Other personnel compensation........	824,000	781,000	-43,000
Special personnel service payments..	1,852,000	1,914,000	+62,000
Total, personnel compensation.....	23,765,000	23,556,000	-209,000
Personnel benefits..................	4,809,000	5,037,000	+228,000
Benefits for former personnel........	18,000	14,000	-4,000
Travel and transportation of persons.	550,000	575,000	+25,000
Transportation of things............	115,000	120,000	+5,000
Rent, communications, and utilities..	4,200,000	4,300,000	+100,000
Printing and reproduction...........	750,000	775,000	+25,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Other Services:			
Consulting services..............	400,000	400,000	---
Other services...................	5,074,000	5,234,000	+160,000
Purchases from Govt.accts........	24,045,000	24,804,000	+759,000
R&D Contracts....................	10,600,000	10,904,000	+304,000
Subtotal, other services...........	40,119,000	41,342,000	1,223,000
Supplies and materials...............	4,000,000	4,200,000	+200,000
Equipment............................	3,916,000	3,372,000	-544,000
Grants, subsidies, & contributions...	336,397,000	350,410,000	+14,013,000
Total budget authority	418,639,000	433,701,000	+15,062,000

NOTE: Includes FTEs associated with HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIA

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	15,846	15,846	15,977	131
11.3	Other than full-time permanent	5,243	5,243	4,884	(359)
11.5	Other personnel compensation	824	824	781	(43)
11.8	Special personnel services payments	1,852	1,852	1,914	62
11.9	Subtotal, personnel compensation	23,765	23,765	23,556	(209)
12.1	Civilian personnel benefits	4,809	4,809	5,037	228
13.0	Benefits for former personnel	18	18	14	(4)
	Subtotal Pay Costs	28,592	28,592	28,607	15
21.0	Travel and transportation of persons	550	550	575	25
22.0	Transportation of things	115	115	120	5
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	4,200	4,200	4,300	100
24.0	Printing and reproduction	750	750	775	25
25.0	Other Services	17,551	15,614	16,205	591
26.0	Supplies and materials	4,000	4,000	4,200	200
	Subtotal non-pay costs	27,166	25,229	26,175	946
	Total Administrative Costs	55,758	53,821	54,782	961

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Significant Items in the House and Senate Appropriations Committees Report

Item	Action Taken or to be Taken
1994 House Report	
Alzheimer's disease	
1. House Report 103-156, page 64, states: "This disease causes enormous hardship for families. . . . The Committee expects NIA to continue its efforts in this area."	1. Alzheimer's disease (AD) continues to be a top research priority for NIA. Recent genetic discoveries have shed new light on the causes and biological mechanisms which result in the development of AD. Genetic factors have been implicated to a much greater extent than previously suspected. Recently, ApoE4, whose gene is located on chromosome 19, has been associated with a greatly increased risk of AD. NIA scientists also hypothesize that early functional and metabolic deficits in AD reflect reversible failure of nerve impulse transmission. Research will continue to study the use of drugs on the course of AD to delay development of morbidity and hospitalization.
Cardiovascular aging	
2. House Report 103-156, page 64, states: "Within the increase provided, the Committee strongly encourages increased efforts in the area of cardiovascular studies within the intramural program at the National Institute on Aging's Gerontology Research Center."	2. The FY 1994 appropriation provided $37.2 million for intramural research, a 3.1 percent decrease below FY 1993 levels. In the distribution of $37.2 million, priority was accorded to the Laboratory of Cardiovascular Science.

Item	Action Taken or to be Taken
Hispanic initiative	
3. House Report 103-156, page 64, states: "Hispanics are the fastest growing and most diverse group among the U.S. elderly. The Bureau of the Census projects that over the next 30 years the Hispanic elderly population will grow at four times the rate of the total elderly population. Moreover, Hispanic elderly have higher poverty rates and are in poorer health than the general elderly population. The committee urges that NIA maintain and strengthen its Hispanic health and aging research initiative."	3. The NIA has recently initiated three additional activities in the area of Hispanic aging: 1) A major international conference on Hispanic elderly day care to provide state of the art information on Hispanic adult day care development, management, and evaluation of cost effectiveness; 2) A national research conference focusing on minority aging issues such as health status, frailty and disability, dementia, and long term care concerns; and 3) A workshop directed toward providing insights into the need for demographic statistics on key variables within the elderly Hispanic population. Outstanding demographers will discuss the development of a future research agenda for the accumulation of significant population statistics.
Demographic research	
4. House Report 103-156, page 64, states: "The Committee is encouraged by ongoing NIA studies, including the Health and Retirement Survey and the Asset and Health Dynamics of the Oldest Old survey, and encourages the continuation of this demographic research."	4. The NIA will continue support for the Health and Retirement Study (HRS), which follows the transitions of persons aged 51-61, in reliance on earned income, private pensions, Social Security, and Medicare benefits. An emerging portrait depicts sharp contrasts between desires for gradual retirement and actual departure from the work force. An auxiliary study of persons aged 70 and older, Asset and Health Dynamics of the Oldest-Old (AHEAD), examines how

Item	Action Taken or to be Taken
	late-life changes in physical and cognitive health affect patterns of saving and income flows. NIA also plans to support up to six new Demographic Centers on Population Aging which apply state-of-the-art demographic, economic, and mathematical methods of analysis on national public policy issues.
1994 Senate Report Osteoporosis research	
1. Senate Report 103-143, page 103, states: "The Committee is very concerned that NIH pay particular attention to the recommendations made by the Office of Technology Assessment in its recent study on menopause regarding the role of exercise and diet in preventing osteoporosis. . . . The Committee expects that NIH will make the study of the relationship of osteoporosis, diet, and exercise a top priority for the Institute."	1. The NIA currently supports many epidemiologic studies, both large and small scale, to determine the role of diet and dietary components in the occurrence of hip fractures as well as in the prevention of bone loss and osteoporosis. NIA also has ongoing intervention trials which are testing: 1) the effect of specific hip exercises in the prevention of bone loss from the hip; and 2) the effect of calcium, vitamin D, and various forms of vitamin D in slowing bone loss in the hip, spine, and other skeletal sites. In FY 1993, the NIA published a Request for Applications (RFA) aimed at elucidating the causes and consequences of the menopausal transition on subsequent health in women. In this multidisciplinary RFA, the NIA encouraged applications which included studies on menopause-related changes in nutrition and physical activity.

Item	Action Taken or to be Taken
Nursing	
2. Senate Report 103-143, page 102, states: "The Committee urges the NIA to continue to collaborate with the National Institute of Nursing Research (NINR) on studies of interventions to manage Alzheimer's disease symptoms."	2. The NIA continues to have a positive collaborative relationship with the NINR in promoting research on care and management of Alzheimer's disease. The NIA, as part of its lead role in the NIH Coordinating Committee for Alzheimer's Disease Research, will be convening a series of research planning workshops, one of which will explicitly address scientific research issues concerning behavioral management and care issues. The NIA will plan and conduct this particular workshop in collaboration with NINR. The proceedings of this workshop, as well as others, will provide the NIA and other institutes, agencies, and private foundations a sound scientific plan for systematic investment in research.
Alzheimer's disease	
3. Senate Report 103-143, page 102, states: "The Committee also believes that NIA should proceed with completion of a long-range plan for harnessing the scientific talent and resources needed to capitalize on the current pace of scientific findings. The broad objectives of this plan should be to slow the rate of deterioration from Alzheimer's by 5 years during the next 5 years, and by 10 years within 10 years. In preparing the plan, the NIA should seek the recommendations of the DHHS Panel on Alzheimer's Disease, the National Institute for Nursing Research and other appropriate institutes, and the Alzheimer's Association."	3. The NIA, through the Office of Alzheimer's Disease Research and the NIH Coordinating Committee for Alzheimer's Disease Research, is in the process of convening a series of research planning workshops aimed at identifying research opportunities and impediments to scientific progress. These workshops will provide a forum for open discussion for the scientific community representing a broad spectrum of disciplines, perspectives and organizations. The proceedings of these workshops will be published by a scientific journal and widely disseminated. The specific recommendations by the

Item	Action Taken or to be Taken
	scientific community will serve as a blue-print for future initiatives in promoting research aimed at accelerating the discovery of possible cause(s) and effective treatments of Alzheimer's disease.
Claude Pepper Older Americans Independence Centers	
4. Senate Report 103-143, page 103, states: "The Committee continues to support increased efforts by the NIA to develop and evaluate innovative approaches to maintaining and increasing independence among older Americans. As the population ages, and particularly as the population of those over the oldest old (those age 85 and older) increases, it is critical that we develop approaches that will both enhance the quality of life for older Americans and reduce health and long-term care costs. The Committee has included additional funds in order to add at least one more Claude Pepper Older Americans Independence Center in fiscal year 1994."	4. The overall FY 1994 budget increase for NIA will allow the addition of at least one more center to be added to the Institute's Claude Pepper Older Americans Independence Center program.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Authorizing Legislation

	PHS Acy Other Citation	U.S. Code Citation	1994 Amt. Authorized	1994 Appropriation	1995 Amt. Authorized	1995 Budget Request
Research and Investigation............	Section 301	42§241	Indefinite	$406,429,000	Indefinite	$421,149,000
National Institute on Aging..................	Title IV, Part C	42§289k-2 - 289k-5	Indefinite		Indefinite	
National Research Service Awards...........	Section 487(d)	42§288	$400,000,000	12,210,000	Such sums as necessary	12,552,000
Total Budget Authority......				418,639,000		433,701,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$135,376,000	$149,067,000 2/	$156,618,000	$156,491,000
1986 Sequester				-6,729,999
1987	145,829,000	174,279,000	179,582,000	177,681,000
1988	156,174,000	203,411,000 3/	199,642,000	194,746,000
1989	204,770,000	225,578,000	210,222,000	222,642,000
1990	229,620,000 4/	241,528,000	245,490,000	242,685,000 5/
1990 Sequester				-3,230,000
1991	248,938,000	278,311,000 6/	377,733,000	323,752,000 7/
1991 Sequester				-4,000
1992	348,558,000	362,528,000	397,176,000	383,382,000 8/
1993	407,284,000	402,218,000	405,218,000	399,924,000 9/
1994	394,156,000	420,303,000	420,303,000	420,303,000
1995	433,701,000 10/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes $4,642,000 in NRSA training programs not considered.

3/ House Allowance consolidated all AIDS activities in OASH.

4/ The 1990 request excludes funds for the National HIV program ($870,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

5/ Excludes enacted administrative reduction of $824,000.

6/ Excludes $9,520,000 in NRSA training programs not considered.

7/ Excludes enacted administrative reductions of $8,020,000 and $1,010,000.

8/ Excludes enacted administrative reductions of $120,000, $2,783,000, and $729,000.

9/ Excludes enacted administration reductions of $3,236,000, $162,000, and $1,146.000.

10/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Extramural Research												
Aging	---	$270,567	---	$323,366	---	$337,021	---	$358,965	---	$373,610	---	+$14,645
Intramural	271	33,118	290	36,721	305	38,259	293	37,170	284	37,537	-9	+367
Research Management and Support	167	19,121	187	21,723	167	23,090	165	22,504	161	22,554	-4	+50
Total, obligations	438	322,806	477	381,810	472	398,370	458	418,639	445	433,701	-13	+15,062
Unobligated balance lapsing	---	+21	---	---	---	+8	---	---	---	---	--	---
Total, Budget Authority	438	322,827	477	381,810	472	398,378	458	418,639	445	433,701	-13	+15,062

Justification

National Institute on Aging

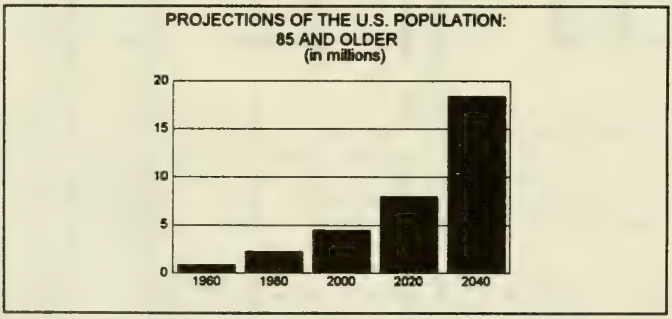
FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
472	$398,378,000	458	$418,639,000	445	$433,701,000	-13	+$15,062,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute on Aging. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Aging (NIA) was created in 1974 to conduct and support research on aging processes with a focus on diseases and other special problems of older people. The remarkable life span that has been realized during this century now presents Americans with three important and related challenges: how to maintain quality of life with advanced age, how to provide cost-effective health care, and how best to divide adult life into working years and retirement years.

The "graying of America," that is, those demographic changes that will occur as the post-World War II baby-boom generation ages, is markedly raising the median age of America's population. The aging of our society will impact health care costs, regardless of the means by which these costs are covered. The over-85 age group is the fastest growing segment of the American population and is often referred to as the "oldest old":



Even with the hope of major advances in the treatment and prevention of debilitating disease, the demand for long-term care is expected to expand dramatically in our society. Research will be pursued on many different aspects of long-term care in general and particularly on new and evolving forms of care. NIA supports research on preventing the need for long-term care or institutionalization, enhancing the quality and efficiency of such care, easing the burden of care, and forecasting the requirements for care.

Alzheimer's disease continues to be a top research priority for NIA. This disease currently affects an estimated four million older Americans and their families, causes enormous personal suffering, and costs the nation at least $90 billion each year. NIA devotes over $200 million annually to Alzheimer's disease research: without the development of new treatments, cures, or preventive approaches to this dreaded disease, the number of individuals and families devastated by Alzheimer's disease will likely increase up to five-fold within the next 50 years.

In addition to Alzheimer's disease, priority initiatives include research on the biology of the aging process and on physical disabilities such as osteoporosis and cardiovascular disease. These initiatives are wide-ranging and can be based on cutting-edge laboratory technologies or upon simple but highly effective strategies such as exercise or behavioral interventions. The goal of NIA-supported research is to understand the basic mechanisms of normal aging and age-associated disease and disability and to translate this basic knowledge into treatment and prevention strategies.

Basic Research on Aging and Associated Diseases

NIA funded basic research is a prerequisite for the rational development of treatment and prevention strategies. Because of the advances from basic aging-related science made possible by NIA support, real hope exists for true increases in independence and active life expectancy, helping to stem the rising cost of health care expenditures. To prevent or cure diseases associated with age such as cancer, cardiovascular disease, osteoporosis, and Alzheimer's disease, we need to continue extensive basic research into their underlying causes as well as to better understand the aging process itself.

For example, research will continue on antioxidants to discover their role and protective action against the damaging effects of naturally occurring "free radicals" on subcellular components. There is increasing evidence that certain nutrients, including vitamin C, vitamin E, and betacarotene, serve as agents of free radical capture and otherwise augment the body's natural protective mechanisms. Any preventive effects of antioxidants would have extraordinary potential for forestalling a wide range of degenerative diseases. With the escalating costs of medical treatment and care for an aging population, simple preventive therapies involving dietary supplementation may have tremendous benefits.

Molecular genetic studies are developing evidence that longevity and cellular senescence (loss of a cell's ability to divide and reproduce itself) are, in part, under genetic control. Characterization of the specific genes which promote longevity and postpone aging and cellular senescence are central to discovering the mechanisms which govern longevity and aging in humans. Knowledge of these fundamental mechanisms will guide and hasten the development of effective prevention and intervention strategies to extend human longevity and health span.

Major breakthroughs have recently occurred in Alzheimer's disease (AD) research that promise to yield definitive results in the near future. Most recently, NIA-supported researchers at Duke University found that a variation of the apolipoprotein E (ApoE) gene, ApoE4, is associated with an unexpectedly high number of AD cases and is probably a major risk factor to developing AD. It is not yet clear how APoE4 affects cellular function. Depending on the results of this research, new diagnostic tests may identify those persons at risk for AD and lead to protective therapies and better outcomes.

Since 60 percent of U.S. deaths are due to vascular disease, NIA has a prime interest in supporting research on age-associated vascular disease. During atherosclerosis, some of the vascular smooth muscle cells (VSMC) begin to multiply and produce proteins which they secrete into their environment. Intramural researchers have discovered that VSMC, when placed in an environment that simulates arterial injury, not only proliferate, but invade membranes and proteins that normally surround the VSMC and the inner lining of blood vessels. Thus, therapeutic measures to prevent this invasion may reduce the extent of the atherosclerotic process, with a significant reduction in vascular disease and in health care costs.

Applied/Clinical Research

NIA supports pre-clinical and clinical treatment research on AD, made possible by past investments in basic laboratory studies. Tacrine, recently approved by the FDA for use in Alzheimer's patients, was tested several years ago in a major clinical trial and found to have an effect in delaying the progress of disease in some patients. However, it provides only temporary relief, and NIA continues its work towards developing and testing new treatments that will allow patients to continue to function independently. NIA is currently testing the drug Deprenyl in combination with the antioxidant vitamin E in a clinical trial. Preliminary results are due by early 1995.

NIA is supporting a number of major clinical initiatives which address the problems of physical frailty and loss of independence that are associated with older persons. Physical frailty is a major cause of long-term care needs and imposes annual costs of at least $54 billion. Results from ongoing NIA-supported studies have provided convincing evidence of the benefits of exercise for maintaining independent function in older persons. FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques) is a set of clinical trials; some interventions have shown more than a 30 percent reduction in fall rates, which could markedly lower the rate of disabling injuries such as hip fractures.

Osteoporosis affects over 25 million Americans, mainly women, and is a serious public health problem since associated fractures are a major cause of disability in older people: costs associated with hip fractures exceed an estimated $7 billion annually. NIA-supported research into new therapies and interventions would impact a very large percentage of the older population and save billions of dollars in health care costs. Recently, attention has focused on treating degenerative conditions such as osteoporosis, osteoarthritis, and muscle atrophy through replacement therapy with "trophic" factors. These factors promote growth and maintenance of tissues such as bone, muscle, and cartilage.

NIA has a keen interest in research particularly relevant to older women. There are many questions surrounding the health implications of menopause and hormonal changes in women and will continue support for a major initiative, the Women's Health and Aging Study, to determine what diseases and other events cause and influence disability in women age 65 years and older. NIA is also committed to research which focuses upon minority subpopulations and the similarities and differences which exist between them and non-minority populations, such as their relative use of long term care services.

These and other initiatives described in the following pages are representative of NIA's broad research portfolio. As we approach the next century, it will be through the continued support of this research that we can develop the means to prevent or cure the major causes of costly disease and disability to maintain good health and independence for older Americans.

The President's appropriation request of $433,701,000 represents current law requirements. No proposed law amounts are included. Funding levels for the National Institute on Aging during the past five years have been as follows:

	Amount	FTE
FY 1990	$238,077,000	401
FY 1991	322,827,000	438
FY 1992	381,810,000	477
FY 1993	398,378,000	472
FY 1994	418,639,000	458

Purpose and Method of Operation

The NIA funds extramural awards through the Aging activity, and operates an intramural research program. Extramural support can be grouped by either: (1) research grants, (2) research training grants, or (3) research contracts. An award mechanism of particular importance to NIA is the research center. NIA center programs are developed in concert with Congressional directives to fill research needs in areas such as Alzheimer's disease, physical frailty, demography, or rural health and aging.

Overall Budget Policy

The NIA FY 1995 request is $433,701,000, an increase of $15,062,000 or 3.6 percent over the comparable FY 1994 level of $418,639,000. The FY 1995 budget will provide $266,620,000 for approximately 953 research project grants. Approximately 272 new and competing research project grants will be awarded. The FY 1995 request provides $56,420,000 to fund 57 research centers; $14,818,000 to fund 185 Other Research awards; and $12,552,000 to support 434 full-time training positions. The FY 1995 request also includes $23,200,000 to fund 69 research contracts; and includes $37,537,000 for intramural research and $22,554,000 for research management and support. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

National Institute on Aging

Extramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$337,021,000	$358,965,000	$373,610,000	+$14,645,000

The research highlights described within this section are extramurally funded through NIA grants and contracts awards.

Funding levels for the extramural Aging activity during the last five years have been as follows:

	Amount
FY 1990	$195,660,000
FY 1991	270,567,000
FY 1992	323,366,000
FY 1993	337,021,000
FY 1994	358,965,000

Rationale for the Budget Request

With the FY 1995 extramural request, these funds will provide support for the Aging activity of $373,610,000, an increase of $14,645,000 or 4.0 percent from the FY 1994 estimate of $358,965,000.

Basic Research on Aging and Associated Disorders

Alzheimer's Disease

Recent genetic discoveries have shed new light on the causes and biological mechanisms which result in the development of Alzheimer's disease (AD). Among the potential causes of AD, genetic factors have been implicated to a much greater extent than was previously suspected. It is now known that mutations in the amyloid precursor protein (APP) gene and in a gene localized to a small region of chromosome 14 account for most inheritance of early onset AD. Late onset AD has been more difficult to trace, but linkage to chromosome 19 was reported in some late onset families. Recently, ApoE4, whose gene is located on chromosome 19, has been shown to be associated with greatly increased risk of AD. This may account for the chromosome 19 linkage reported earlier. More significantly, the ApoE4/AD association has been found not just in late onset families but also in the general population. The increased risk associated with ApoE4 could account for many AD cases previously designated "sporadic."

Larger epidemiological studies are necessary to confirm the association of ApoE4 with AD. Should ApoE4 be found to be a major factor in determining

AD susceptibility, modification of ApoE activity would become an attractive target for development of therapeutics. Ultimately, the elucidation of the complete molecular pathway which results in the development of AD will allow the design of optimal pharmacological treatment and prevention strategies.

Risk Factors Associated with AD

One of the long range goals of AD research is to determine the full range of risk factors for AD which will lead to a more complete understanding of its etiology. A major theme of epidemiological research in Alzheimer's disease is to address specific biomedical problems in minority and other distinct population groups in an effort to extend knowledge about age-specific incidence, prevalence rates, and risk factors for the onset of AD. Three studies have recently been initiated in African-American populations. The major purpose is to identify and clarify the risk factors for Alzheimer's disease and multi-infarct dementia (MID) in three groups of patients: those with Alzheimer's disease, those with MID, and those with multiple strokes but without evident cognitive dysfunction. The investigation will provide important new information about risk and protective factors for cognitive and functional decline in older African-Americans. NIA also supports the Honolulu Dementia Study. The objectives of this study are to determine rates and risk factors for Alzheimer's disease and vascular dementia in aging Japanese-American men.

Sleep

As many as half of the older population suffer from chronic sleep disturbance, a condition that frequently leads to problematic use of sedative medication, reduced quality of life, and increased morbidity and mortality. NIA supported studies on sleep disorders, such as the multi-center "Established Populations for the Epidemiologic Study of the Elderly" (EPESE), provide support for the effective detection, treatment, and prevention of sleep disorders. Data generated from EPESE have shown that sleep disorders are often associated with poorer self-perceived health, increased depressive symptoms, physical disability, respiratory symptoms, and over-the-counter medication use. Treatment and prevention of sleep disorders can result in savings in health expenditures as well as enhancing the quality of life of older persons.

Control of Cell Proliferation in Aging and Cancer

Regulation of cell proliferation is required to maintain the human body's equilibrium. NIA research has provided a greater understanding not only of normal cell proliferation but also the causes and effects resulting from cell senescence--the loss of proliferative capacity--or the opposite, uncontrolled proliferation seen in cancer. Understanding these biological mechanisms will further our knowledge of normal aging and cancer at the cellular level and promises to provide key contributions to unravelling the fundamental mechanisms underlying the aging process and other age-related diseases in the near future.

Research progress is currently being made in several areas. Two NIA-funded laboratories have independently obtained evidence that p53, a tumor suppressor protein, induces expression of another protein which binds to kinases, a class of enzyme, and inhibits their function. The activity of these kinases is essential for replication. Further research will reveal the mechanisms of these reactions with the ultimate goal of designing drugs which can restore this tumor suppressive property.

A second protein of interest to both aging and cancer research is a protein known as bcl-2, which inhibits a natural process known as programmed cell death. If this programmed death is inhibited the result will be overpopulation of cells, as in cancer. This is also thought to be one explanation for benign prostatic hypertrophy. The mechanism for controlling bcl-2 expression needs to be elucidated, opening up the possibility of interventions to regulate bcl-2 when needed.

A third area of interest to both aging and cancer research is the role of telomere shortening in controlling cell proliferation. Telomeres are repeated DNA sequences found at the ends of chromosomes that shorten each time a cell divides. A very recent working hypothesis is that telomeres shorten because of the "end-replication problem," and that continued proliferation requires some as yet undefined minimal telomere length. The implications of this research are that both senescence and cancer could be regulated by developing interventions which either prevent telomere shortening or inhibit telomerase activity.

Role of Oxidative Damage in Aging

"Free oxygen radical" damage has long been believed to be a risk factor for the degenerative processes which accompany aging. These compounds can damage DNA, proteins, and lipids. The resulting damage can lead to cancers or dysfunctional proteins and damaged membranes which lessen a cell's ability to carry out its proper function. There is increasing evidence that certain micro-nutrients, including vitamins C and E, serve as agents of free radical capture or "antioxidants," and augment the body's protective mechanisms. The preventive effects of antioxidants have potential for forestalling a range of degenerative diseases. There appears to be a role for dietary antioxidants in the prevention of some cancers, senile dementias, and cardiovascular diseases. Simple preventive schemes involving dietary supplementation could lead to significant savings in the costs associated with medical treatment.

Biology of Aging Muscle

A decrease in mass and functional capability of skeletal muscles contributes substantially to the impairment of locomotive performance that accompanies human aging and is a significant risk factor for physical frailty. NIA continues to support basic research into the molecular basis of skeletal muscle growth, age-related muscle degeneration, and selective fiber atrophy. The development of effective intervention strategies to retard or prevent age-related muscle degeneration is dependent on basic research to delineate the underlying mechanisms. Such interventions would be expected to significantly extend human health span, reduce frailty, and increase independence and quality of life for older adults.

Protein Structure and Function

NIA is also focusing efforts on determining the structures of proteins which have undergone non-hereditary changes to their amino acids. For many years it has been clear that "modified proteins" accumulate during aging and may interfere with normal cellular processes. These unstable proteins lead to such age-related problems as cataracts, interrupted blood flow to the heart and brain, failure of the immune system, impaired ability to heal wounds, and loss of cognitive function. NIA is attempting to discover the mechanisms by which modification of proteins occurs, why they accumulate in aging, and the physiological consequence of these changes. Understanding these mechanisms may ultimately lead to effective treatment and prevention strategies.

Clinical and Applied Research on Aging and Associated Disorders

Treatment of Alzheimer's Disease (AD)

The primary manifestation of AD dementia is intellectual/cognitive deterioration and the sole drug currently on the market, Tacrine, provides only temporary relief for treatment of AD. In FY 1991, the Drug Discovery Groups in AD program was initiated to facilitate the pre-clinical development of new compounds for treating Alzheimer's disease by expanding the range of approaches to drug treatment beyond the current focus. The research activities of three of the Groups deal with attempts to circumvent the blood brain barrier's ability to keep out peripherally administered peptides and proteins. This is important because one potential treatment for AD would be to raise the concentration in the brain of neurotrophic factors which promote the health and well being of neurons. Since neuron death and dysfunction is a major problem in Alzheimer's disease, these factors may be effective in delaying or reversing cognitive and behavioral symptoms of AD.

Behavioral Aspects of AD

NIA also supports research aimed at ameliorating those alterations in behavior, mood, and function which are frequently the aspects of the disease that cause the greatest stress for family members and difficulties for both professionals and family members in providing optimal care. It is important to provide tools for families and nursing homes which will replace physical and pharmacological restraints. The goal is to reduce the severity and frequency of disruptive behavior, to allow patients to live in the least restrictive environment and manner, to maximize dignity and independence, and to retain or reestablish self-care practices.

NIA supports several research projects examining the extent, causes, and consequences of caring for people with AD and related dementias. These include ten coordinated research projects to examine the nature and outcomes of special care units for persons with dementia. Other activities include initiatives in family caregiving and health services, burdens of care research in special populations, specifically minority family caregivers; supportive environments and everyday functioning; and demographic and economic aspects of Alzheimer's disease.

In 1991, the NIA, in conjunction with the National Institute for Nursing Research and the Alzheimer's Association, began fourteen pilot feasibility studies for new and innovative methods for managing the behavioral symptoms associated with AD. The symptoms of special concern included wandering, disturbed sleep, pacing, agitation, feeding and dressing difficulties, incontinence and toileting difficulties, screaming and other vocalizations, aggression and violence, and inappropriate sexual behavior. Studies were specifically sought for strategies to enhance AD patients' self-care abilities and activities of daily living. These feasibility studies will lay the scientific and clinical groundwork that may lead to large-scale clinical studies/trials on the assessment and nonpharmacologic management of secondary symptoms and disabilities.

Language, Attention and Cognition

Cognitive dysfunction in aging is defined by the changes in neural and psychological processes that control or regulate attention, memory, thought, communication, spatial competence, decision making, and other cognitive processes. Ongoing studies are being conducted to explore the range of normal and abnormal cognitive processing. A particularly exciting development is the use of neuroimaging techniques that permit researchers to image the brain while cognitive processing occurs. These techniques hold great promise for isolating brain structures which control various aspects of cognitive function and for determining what parts of the brain are controlling age-related changes in cognitive function.

Frailty and Physical Functional Independence

Physical frailty is a major cause of long-term care needs and afflicts over 3.25 million older Americans. Epidemiologic studies have shown a relationship between impairment and strength, endurance, gait, and the occurrence of loss of independence. FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques) is an NIA supported set of clinical trials which have demonstrated that fall rates in moderately frail older persons can be reduced significantly by interventions targeted to individuals' specific fall risk factors. Other findings show that balance, strength, and endurance training can markedly improve physical performance abilities in a wide variety of older populations ranging from relatively healthy community-dwelling persons to very frail nursing home residents. Other research has demonstrated that the administration of growth hormone has been associated with arresting or reversing degenerative tissue changes which decrease strength and mobility.

Claude D. Pepper Older Americans Independence Centers

The NIA added one new Claude D. Pepper Older Americans Independence Center (OAIC) in fiscal year 1993 and plans to add at least one additional center in fiscal year 1994. The OAICs were authorized by Congress to promote research on interventions that can help older people live independently, and avoid institutionalization or prolonged hospitalization. Besides testing specific ways to prevent disability, the OAICs train additional researchers capable of doing such studies and disseminate information on successful interventions to clinicians and the general public.

Cardiovascular Disease

Cardiovascular diseases and stroke account for more deaths in the population 75-84 years old than the next nine leading causes of death together. Cardiovascular diseases associated with aging include hypertension, stroke, ischemic heart disease, heart failure, peripheral vascular disease, cardiac arrhythmias, and impairments in blood pressure regulation which cause intermittent hypotension. The incidence and prevalence of these conditions rise with age.

NIA supported investigators at the Claude Pepper Center at Harvard have shown that a reduction in overall heart rate variability is associated with aging, congestive heart failure, coronary artery disease, sudden death syndromes, and after-meal low blood pressure. Although the average heart rate did not differ between the age groups or sexes, heart rate variability was greater in women than men at all ages. The increase in heart rate variability in women compared to men may be related to lower cardiovascular disease risk and greater longevity in women. Future studies are needed to gain a better understanding of this and other mechanisms by which age and gender contributes to cardiovascular diseases. NIA plans a significant research initiative in this area for fiscal year 1994.

Osteoporosis and Bone Quality

The progressive loss of bone, which is universal after middle age, very commonly leads to osteoporosis, a condition characterized by increased skeletal fragility. NIA supports a range of research into the causes and treatment of osteoporosis. Research aimed at identifying markers and risk factors that predict changes in bone mass, bone competence, and fracture susceptibility is of vital importance in identifying individuals at risk and in evaluating the effectiveness of treatment strategies.

For example, while diabetes has been hypothesized to be a risk factor for bone loss and osteoporosis, recent research has shown that some diabetic women actually had increased bone mass compared to non-diabetic women. This distinction did not appear among men. This gender-related difference suggests that certain hormonal agents could play a potentially important role as risk factors and/or in a therapeutic strategy to preserve bone mass. Additional research has uncovered a link between cigarette smoking and reduced bone mass in the hip. These findings are particularly important, not only in light of the public health implications, but because they also apply to men, in whom the need for research on risk factors for osteoporosis has received little attention.

The decrease in estrogen levels which follows the onset of menopause frequently results in rapid bone loss which often precedes osteoporosis. Recent research has discovered that osteoclasts (cells that break down and remove bone) are target cells for estrogen, and that estrogen directly inhibits the breakdown of bones by osteoclastic cells. This finding will encourage the development of new approaches which will be effective in halting bone breakdown and hence preventing osteoporosis.

Menopause and Post-menopausal Problems

Menopause is a universal event in female aging and is also associated with an acceleration in the rate of bone loss. However, it is unclear whether osteoporosis in old age is greater in women who had a relatively early menopause compared to those whose menopause was later. Recently, a study has shown that the total number of reproductive years may be a significantly more sensitive index for identifying women at increased risk of osteoporosis. In order to gain an increased understanding of the inter-relationship between menopause and osteoporosis and other problems associated with menopause, NIA began a major initiative in this area in fiscal year 1994. Because the menopausal experience in minority women has been particularly neglected, special emphasis in minority populations is an integral part of this initiative.

NIA also continues to support the NIH Women's Health Initiative, which includes 70,000 post-menopausal women ages 50-79. This study is intended to assess the long term benefits and risk of hormone therapy as it relates to cardiovascular disease, osteoporosis, and breast and uterine cancer. Related to this effort, NIA began the Women's Health and Aging Study which is exploring the causes and course of physical disability in women aged 65 and older. The study will also provide important information on how the disease-disability relationship is modified by cognitive functioning; on psychological factors; and on social, economic, and medical resources of older women.

Failure to Thrive and Malnutrition

The "failure to thrive" syndrome consists of weight loss, decreased appetite, poor nutrition, and inactivity. It is often accompanied by dehydration, depressive symptoms, impaired immune function, and low serum cholesterol. NIA actively encourages research to develop interventions designed at preventing, arresting, or reversing the failure to thrive syndrome. NIA is also interested in research on a variety of dietary disorders in older persons, especially malnutrition and the role of nutrition in overall health status in old age. There is a great deal of conflicting information on dietary recommendations for older people, leading to inappropriate use of dietary supplements and potentially harmful eating habits. Research in this area can lead to the development of scientifically sound guidelines for older people, particularly those relating to medications or to diseases that may require dietary changes to maintain functioning.

Improving Long Term Care for the Elderly

Recent discussions of health care reform emphasize research in regard to long-term care needs. Identifying factors that subsequently lead to placement in nursing homes (NH) is of particular importance for recognizing those at risk and then developing interventions that can minimize, if not eliminate, associated risks. NIA research provides valuable information for predicting NH placement and mortality. These analyses confirmed the predictability of several key sociomedical risk factors--living alone, having fewer non-kin social supports, low sense of personal control, and other functional limitations.

The NIA Special Care Initiative Study predicts, examines, and evaluates the use of long term care services and practices, and identifies strategies for modifying and improving services for those in need. The idea behind a Special Care Unit (SCU) is that people with dementia might benefit from specially designed programs or environments that are different from those provided in a traditional nursing home setting. While special care units have proliferated across the country in recent years, very little is known about their effectiveness in caring for Alzheimer's patients, in relieving burdens of care for the patient's family, or how these programs compare to traditional nursing home care in terms of costs and effectiveness. The NIA Special Care Unit Initiative projects are designed to evaluate the impact of these new care units on people with Alzheimer's disease, their families, and nursing home staff. These studies will provide the public, nursing home facilities personnel, and policy makers with the first comprehensive look at how special care units work.

Self-care refers to a broad range of activities undertaken by an individual to maintain or promote health, as well as to detect, prevent and treat common health problems and conditions. Research being conducted in this area seeks to assess the extent and nature of self-care practiced by older adults, the strategies used to maintain independence, the relationship between self-care and other forms of care, and the subsequent use and costs of health care.

Economic and Health Status of the Elderly

The well-being of America's elderly clearly depends on their economic and health security. The reciprocal and multidimensional relationship between income and health in adult life is poorly understood; almost nothing is known about the effects of these transitions at advanced ages.

Two major new NIA-supported studies aim to clarify how people experience and evaluate their health and economic status from immediate pre-retirement years to very old age. The Health and Retirement Study (HRS) follows transitions in reliance on earned income, private pensions, Social Security, Medicare benefits, etc. in an initial sample of over 12,000 persons aged 51-61 years. An emerging portrait of this population depicts sharp contrasts between desires for gradual retirement and actual departure from the work force. The role of health and disability in the timing of retirement, and of retirement in the health and economic well-being of this cohort, are also being examined. An auxiliary study, Asset and Health Dynamics of the Oldest-Old (AHEAD), follows 7,300 persons aged 70 years and over--almost a third of them over age 80--to examine how late-life changes in physical and cognitive health affect, and are affected by, patterns of saving and income flows.

NIA also plans to support up to six Demographic Centers on Population Aging which apply state-of-the-art demographic, economic, and mathematical methods to analyses of these and other new databases, providing timely reports on national public policy issues. The Centers will include outreach activities that benefit researchers at many institutions across the nation.

Aging and Family Life

Family based research identifies how health, illness, and disability in later life are affected by intergenerational exchanges, informal caregiving for frail elders, and cultural/ethnic diversity in family relationships. These relationships are pivotal to the health and health care of older people. This research contributes to an understanding of adequacy of informal care for frail elders and of the factors that determine the use of health care services by older people and their caregivers. In advancing basic social science research, family aging studies seeks an understanding of interpersonal relationships in physical and emotional health and illness across the life span.

Special Populations

The NIA continues to be committed to minority populations, women, and rural older populations. Most recently, the Institute began a research effort to establish Exploratory Centers for Research on Health Promotion in Older Minority Populations. These centers will conduct pilot research and plan for a program of medical, behavioral, and social research; medical and pyschosocial interventions; and programs of health education and community outreach aimed at improving the health status of older ethnic minority populations.

NIA is vigorously expanding its minority research focus and minority participation in all of its research initiatives. For example, investigators are testing intervention strategies to prevent frailty in older black and Hispanic-American populations and focusing on health conditions such as hypertension, diabetes, and prostate cancer, which are disproportionately prevalent in older Americans. NIA also supports four rural health centers established to explore the special health needs of older rural Americans, including access to and results of health care services.

National Institute on Aging

Intramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
305	$38,259,000	293	$37,170,000	284	$37,537,000	-9	+$367,000

The Intramural Research Activity funds research conducted by government scientists at the Gerontology Research Center (GRC) located in Baltimore, Maryland, and at the NIH Clinical Center. This activity also supports the operation of NIA's Epidemiology, Demography, and Biometry Program.

Funding levels for the Intramural Research Activity for the past five years are as follows:

	Amount	FTE
FY 1990	$27,947,000	253
FY 1991	33,118,000	271
FY 1992	36,721,000	290
FY 1993	38,259,000	305
FY 1994	37,170,000	293

Rationale for the Budget Request

The FY 1995 budget request for Intramural Research is $37,537,000, an increase of $367,000 over the FY 1994 estimate of $37,170,000.

The long-term goals of the NIA intramural research program (IRP) are: 1) to conduct basic research relevant to understanding aging processes and age-associated disabilities; and 2) to develop interventions to prevent or retard age-associated diseases and disabilities. The IRP conducts the landmark Baltimore Longitudinal Study of Aging and is a major setting for post-doctoral training of promising investigators.

Intervening in Aging Processes

The causes of aging are complex and involve both internal and environmental factors that damage molecules, cells, and tissues as well as the ability of the host to resist and repair such damage. IRP scientists, using the latest techniques of molecular and cellular biology, continue to search for the causes of aging and ways to retard and reverse age-associated deficits before they progress to disease, disability, and institutionalization. Current projects include: 1) investigations of DNA repair in genes including those with implications in malignancy and longevity; 2) research on the mechanisms by which the death of cells is increased with age and diseases such as Alzheimer's disease and osteoarthritis; 3) studies on the loss of host defenses to aging; and 4) the potential use of gene therapy to prevent or reverse age deficits or diseases.

Regarding the immune system, it is well known that many older individuals show an impaired immune response that puts them at greater risk of infections. NIA and National Cancer Institute scientists have defined a novel cell surface protein that is essential for immune activation. Better definition of the molecular components in the immune response offers new possibilities for enhancing appropriate and suppressing inappropriate immunologic reactions.

Baltimore Longitudinal Study of Aging (BLSA)

The BLSA, begun in 1958, seeks to understand how and why we age. The study panel is a group of over 1,100 highly dedicated women and men, from 20 to 97 years of age, who have volunteered to come to Baltimore every two years for intensive study to establish their physiologic and psychologic status. Over 160 new participants have been recruited as part of a multi-year strategy to enroll 350 more women and minorities, meeting specific health criteria, for major initiatives with hypotheses about gender and racial differences. Biologic samples are collected from participants at sequential visits and banked which, with the extensive health and behavioral data assembled over time, allows "instantaneous longitudinal studies" to be conducted. These studies would otherwise take a decade or more to complete and cost millions of dollars. Initial research projects using a newly established DNA bank include studies of age-associated changes in DNA repair and preferential DNA repair in breast cancer. A vascular initiative is examining age, race, and gender differences in blood pressure, arterial stiffness, thickening of the heart muscle and the relationship of these parameters to heart and vascular disease. The BLSA Perimenopausal Study is characterizing the biological and psychosocial antecedents of the menopausal transition in 200 women.

Alzheimer's Disease (AD)

The IRP has a focused research program on the etiology, diagnosis, and treatment of AD. The distinctive aspect involves applying and refining sophisticated technologies--positron emission tomography, magnetic resonance imaging, and spectroscopy--to study patients throughout the disease course to yield new insights. For example, NIA scientists have devised new ways to evaluate drug efficacy using only a few patients by studying the longitudinal "trajectory" of function and pathology in individual patients. These are being applied in studies to evaluate sites and mechanisms of action in AD. NIA scientists have hypothesized that early functional and metabolic deficits in AD reflect reversible failure of nerve impulse transmission. Research will continue to study the use of drugs on the course of AD to delay development of morbidity and hospitalization. NIA scientists have also shown that biopterin, a natural compound that regulates many fundamental brain mechanisms, is reduced in the cerebrospinal fluid of certain AD patients. A clinical trial has been initiated to study the possible role of biopterin in the pathophysiology of AD and of its potential as a therapeutic agent.

Vascular Disease

A major ongoing intramural program studies age-associated vascular disease such as atherosclerosis, hypertension, and stroke. NIA studies show that older men and women with higher fitness levels generally have arteries which are less stiff than those of less fit individuals. These results suggest that the age-associated increase of arterial stiffness may be slowed by aerobic exercise; longitudinal follow-up is underway. Researchers have found that, with age, vascular smooth muscle cells become highly motile and invasive and produce degradative enzymes that destroy normal blood vessel architecture and weaken the blood vessels. Various compounds have been found to stabilize the dedifferentiation of the smooth muscle cells and further research will continue on these prototype drugs. Other opportunities that are being pursued include: 1) the use of gene therapy as a potential new approach to the treatment of coronary artery disease; 2) studies of the relationship between hypertension associated with stress and high sodium intake, particularly in minorities; and 3) insights into the basic cellular and molecular mechanisms contributing to renarrowing of an artery following balloon dilation.

Frailty, Osteoporosis, Hormone Replacement Therapy and Women's Health

Issues of women's health and well-being command special attention within the IRP and include the following emphases: First, a decline in growth hormone (GH) levels parallels the loss of muscle as well as the development of frailty. Recent intramural studies show that a natural stimulator of growth hormone production, growth hormone releasing hormone, restores the normal pattern and level of GH in older individuals. Significant increases in muscle strength were apparent after six weeks of treatment suggesting that such factors could be utilized to reverse certain age-associated diseases and disabilities. If successful, this therapeutic approach could speed recovery and reduce bed days and hospital costs. Also, a collaborative trial is underway comparing the effects of replacement of GH and a gender appropriate sex steroid in 160 women and men. This will enable the effects of hormone therapy on a wide variety of relevant health variables to be compared in women versus men. A National Institute for Nursing Research and NIA collaborative intramural program will continue to examine post-operative complications from hip fracture and devise behavioral nursing interventions to enhance outcomes.

Diabetes and Other Age Associated Metabolic Defects

NIA conducts a multifaceted research effort to develop new therapies that are safe and specific for the control of blood glucose in older diabetic patients to prevent the disease's late complications. Significant progress has been made in defining and modifying the regulatory signals controlling pancreatic insulin secretion. NIA scientists have found that the action of insulin can be enhanced and prolonged by preventing the removal of phosphate from the activated form of the insulin receptor. These results are being aggressively pursued given their promise for opening new avenues in the treatment of diabetes associated with aging.

Longitudinal Studies of Prostate Disease and PSA

Collaborative studies will continue to investigate potential uses of rates of change in prostate-specific antigen (PSA) levels to improve clinical detection of prostate cancer and benign prostatic hyperplasia (BPH). Recent findings suggest that: 1) rates of change of PSA are significantly more accurate than the traditional single measure for the early detection of prostate cancer; 2) certain PSA criteria now in use may lead to many unnecessary prostate biopsies and should be dropped from clinical practice; and 3) PSA tests may be useful in guiding optimal treatment decisions for BPH.

National Institute on Aging

Research Management and Support

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
167	$23,098,000	165	$22,504,000	161	$22,554,000	-4	+$50,000

The research and management support (RMS) activity provides administrative support and scientific management for the grants and contracts awarded under the aging activity, as well as for overall program direction and policy development.

Funding levels for the Research Management and Support activity during the last five years have been as follows:

	Amount	FTE
FY 1990	$14,470,000	148
FY 1991	19,142,000	167
FY 1992	21,723,000	187
FY 1993	23,098,000	167
FY 1994	22,504,000	165

Rationale for the Budget Request

The FY 1995 budget request for RMS is $22,554,000, an increase of $50,000 from the FY 1994 current estimate of $22,504,000.

The extramural initiatives supported by NIA have been developed and are managed by the extramural program staff funded by the RMS activity. Scientific staff members focus their efforts on developing research initiatives, reviewing, awarding, and administering grants/contracts on aging research and training to universities, hospitals, medical centers, and other organizations. The RMS mechanism also provides funding for facility support costs, related expense items essential to all research programs, and the mandated Alzheimer's Disease Education and Referral (ADEAR) Center which gathers, maintains, and disseminates information on Alzheimer's disease research and services. The center operates a toll-free telephone number to provide the latest information and referral services to health professionals. The NIA has developed a national health education campaign to inform health professionals and the public about the importance of the pneumococcal pneumonia vaccine. Direct support is also provided for the operation of several interagency coordinating committees related to aging research; NIA is chair or co-chair of these committees which include the Federal Forum on Aging, the DHHS Advisory Panel on Alzheimer's Disease, and the Task Force on Aging Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Appropriation	1995 Estimate
Office of the Director	77	76	75
Biology of Aging Program	14	14	13
Behavioral and Social Research Program	16	16	15
Geriatrics Program	9	9	9
Neuroscience and Neuropsychology	15	15	14
Office of Extramural Affairs	36	35	35
Epidemiology, Demography, and Biometry Program	19	18	17
Intramural Research Program	286	275	267
	472	458	445

Average GS/GM Grade

1990	10.50
1991	10.12
1992	10.44
1993	10.33
1994	10.30
1995	10.26

NOTE: Includes FTEs associated with HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1995 Budget

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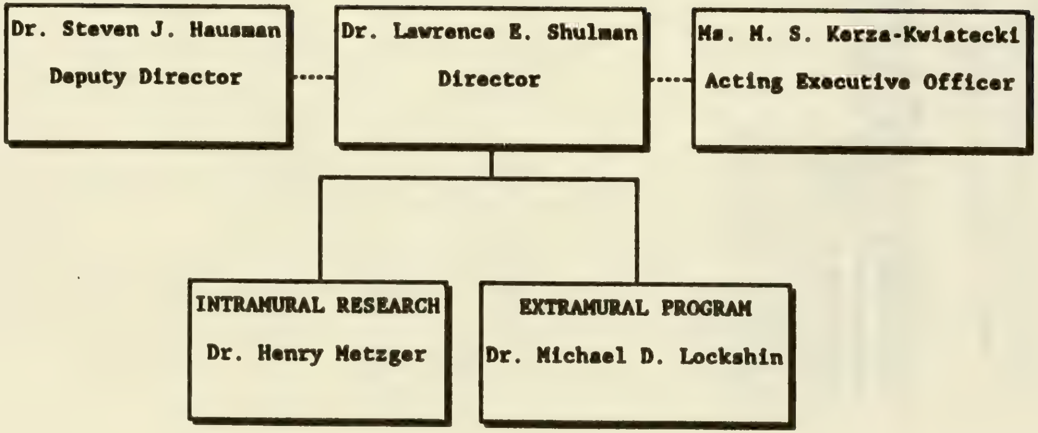
NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to arthritis and musculoskeletal and skin diseases, [$223,280,000] $228,413,000 *of which $2,422,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriation Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Language Analysis

Language Provision	Explanation
".....of which $2,422,000 shall not become available for obligation until September 19, 1995."	To ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$214,619,000	$223,280,000	$228,413,000
Investment initiatives			
Section 511 .. 8% Reduction	-1,717,000		
Section 513 Consultant Services reduction	-5,000		
Section 216 Salary & Expense reduction	-441,000		
Subtotal, adjusted appropriation	212,456,000	223,280,000	228,413,000
Real transfer to NIAID for Tuberculosis research	-209,000		
Comparative transfer to Office of AIDS Research for HIV activities	-1,760,000	-2,795,000	
Subtotal, adjusted budget authority	210,487,000	220,485,000	228,413,000
Unobligated balance, lapsing	-39,000		
Total, obligations	210,448,000	220,485,000	228,413,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1993 -- $2,266,000; FY 1994 -- $2,618,000; FY 1995 -- $2,618,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants						
Research projects:						
Noncompeting....................	530	$111,555,000	506	$111,325,000	488	$111,089,000
Administrative supplementals....	(21)	556,000	(22)	796,000	(22)	828,000
Competing:						
Renewal........................	63	15,000,000	66	17,167,000	73	19,590,000
New............................	98	15,313,000	106	18,230,000	118	21,593,000
Supplemental...................	2	68,000	2	170,000	2	194,000
Subtotal, competing............	163	30,381,000	174	35,567,000	193	41,377,000
Subtotal, research projects...	693	142,492,000	680	147,688,000	681	153,294,000
Research centers:						
Specialized/Comprehensive.......	28	23,436,000	30	25,942,000	30	27,008,000
Other Research:						
Research career programs........	64	5,066,000	65	5,076,000	65	5,218,000
Cooperative Clinical Research...		200,000		200,000		200,000
Minority biomedical research support..............		420,000		430,000		452,000
Other research related..........	23	1,802,000	28	1,924,000	28	1,984,000
Subtotal, other research......	87	7,488,000	93	7,630,000	93	7,854,000
Total, research grants...........	808	173,416,000	803	181,260,000	804	188,156,000

Training:						
Individual awards:						
Noncompeting..................	21	713,000	27	826,000	26	817,000
Competing.....................	14	384,000	9	274,000	10	314,000
Subtotal, individual..........	35	1,097,000	36	1,100,000	36	1,131,000
Institutional awards:						
Noncompeting..................	170	5,093,000	181	5,549,000	164	5,214,000
Competing.....................	13	419,000	22	721,000	39	1,240,000
Subtotal, institutional.......	183	5,512,000	203	6,270,000	203	6,454,000
Total, training...................	218	6,609,000	239	7,370,000	239	7,585,000
Research & development contracts..	20	3,332,000	17	4,491,000	18	4,817,000
	FTE		FTE		FTE	
Intramural research...............	82	17,298,000	77	17,566,000	77	17,830,000
Research management and support...	84	9,832,000	73	9,798,000	73	10,025,000
TOTAL BUDGET AUTHORITY, NIAMS.....	166	210,487,000	150	220,485,000	150	228,413,000
Clinical Trials...................		(6,960,000)		(7,617,000)		(7,990,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes

1994 Estimated budget authority	$220,485,000
1995 Estimated budget authority	228,413,000
Net Change	+7,928,000

	1994 Current Estimated Base		Change from Base	
	FTE	Budget Amount	FTE	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Research Program:				
a. Within grade increases		$5,569,000		+$64,000
b. Annualization of 1994 locality pay increases		5,569,000		+48,000
c. 1995 Pay raise		5,569,000		+74,000
d. One Less Day of Pay		5,569,000		-21,000
e. Federal Employees Compensation Fund		5,569,000		+6,000
f. Payment for centrally furnished services		6,014,000		+247,000
g. Increased costs of laboratory supplies, materials, and other expenses		5,983,000		+68,000
h. Service and supply fund increase		5,983,000		+109,000
Subtotal				+595,000
2. Research Management and Support:				
a. Within grade increases		4,815,000		+69,000
b. Annualization of 1994 locality pay increases		4,815,000		+38,000
c. 1995 Pay raise		4,815,000		+66,000
d. One Less Day of Pay		4,815,000		-18,000
e. Payment for centrally furnished services		2,283,000		+177,000
f. DHHS Working Capital Fund		206,000		+2,000
g. Increased costs of supplies, materials, and other expenses		2,700,000		+31,000
h. Service and supply fund increase		2,700,000		+46,000
Subtotal				+411,000

B. Program:	No.	Amount	No.	Amount
1. Research Project Grants:				
a. Noncompeting.............	506	112,121,000	-18	-204,000
b. Competeting...............	174	35,567,000	+19	+5,810,000
	680	147,688,000	+1	+5,606,000
2. Research Centers:	30	25,942,000	0	+1,066,000
3. Other Research:	93	7,630,000	0	+224,000
4. Training:	239	7,370,000	0	+215,000
5. R & D Contracts:	17	4,491,000	+1	+326,000
	FTEs			
6. Intramural Research Program: Administrative Cost Reduction..................	77	17,566,000	0	-331,000
7. Research Management and Support: Administrative Cost Reduction..................	73	9,798,000	0	-184,000
				+6,922,000
Total changes............				+7,928,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment....	150	150	---
Full-time equivalent of overtime and holiday hours.......	2	2	---
Average SES salary..................	$105,950	$107,645	+$1,695
Average GM/GS grade..................	10.5	10.5	0
Average GM/GS salary.................	51,000	52,500	+1,500
Average salary, grades est. by act of July 1, 1944 (42 USC 207)..........	74,000	75,000	+1,000
Average salary of ungraded positions.	---	---	---

	1994 Appropriation	1995 Estimate	Increase or Decrease
Personnel Compensation:			
Full-time permanent................	$5,376,000	$5,534,000	+$158,000
Other than full-time permanent.....	1,977,000	2,035,000	+58,000
Other personnel compensation.......	360,000	371,000	+11,000
Special personnel services.........	905,000	931,000	+26,000
Subtotal, personnel compensation.	8,618,000	8,871,000	+253,000
Personnel benefits..................	1,766,000	1,818,000	+52,000
Benefits for former personnel........	---	---	---
Travel and transportation of persons.	318,000	329,000	+11,000
Transportation of things.............	41,000	44,000	+3,000
Rent, communications and utilities...	281,000	289,000	+8,000
Printing and reproduction............	227,000	209,000	-18,000

NOTE: Includes FTEs associated with HIV Research Activites. Funds to support these FTEs are included in the NIH Office of AIDS Research.

	1994 Appropriation	1995 Estimate	Increase or Decrease
Other Services:			
Consulting Services	236,000	243,000	+7,000
Other services	2,151,000	1,773,000	-378,000
Purchases fr. Govt. Accts	10,532,000	10,970,000	+438,000
Operation of GOCOs	240,000	267,000	+27,000
R & D Contracts	3,942,000	4,268,000	+326,000
Supplies and materials	1,729,000	1,698,000	-31,000
Equipment	1,774,000	1,893,000	+119,000
Grants, subsidies and contributions	188,630,000	195,741,000	+7,111,000
TOTAL	220,485,000	228,413,000	+7,928,000

National Institutes of Health
Administrative Costs
Budget Authority
NIAMS

Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
Personnel Compensation:				
11.1 Full-time permanent	5,376	5,376	5,534	158
11.3 Other than full-time permanent	1,977	1,977	2,035	58
11.5 Other personnel compensation	360	360	371	11
11.8 Special personnel services payments	905	905	931	26
11.9 Subtotal, personnel compensation	8,618	8,618	8,871	253
12.1 Civilian personnel benefits	1,766	1,766	1,818	52
13.0 Benefits for former personnel	0	0	0	0
Subtotal Pay Costs	10,384	10,384	10,689	305
21.0 Travel and transportation of persons	245	318	329	11
22.0 Transportation of things	71	41	44	3
23.2 Rental payments to others	0	0	0	0
23.3 Communications, utilities, and miscellaneous charges	372	281	289	8
24.0 Printing and reproduction	73	227	209	(18)
25.0 Other Services	12,775	11,581	11,675	94
26.0 Supplies and materials	1,664	1,729	1,698	(31)
Subtotal non-pay costs	15,200	14,177	14,244	67
Total Administrative Costs	25,584	24,561	24,933	372

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1994 House Report	
1. Systemic Lupus Erythematosus (SLE) The House in its report 103-156, page 65, stated: "...NIAMS has placed a high priority on lupus, a disease which is more prevalent among women, and especially among minorities. Its research activities include expanding knowledge of the basic causes of lupus, developing innovative treatments that are less toxic than current treatments, and exploring the scientific reasons why lupus is more prevalent in women and minorities. Within the increased funding provided, the Committee encourages NIAMS to increase its research in this area."	1. Support for research on lupus remains a very high program priority for NIAMS. As a result of recent Institute initiatives, the NIAMS is supporting: two Specialized Centers of Research on Lupus; basic research in molecular biology investigating the causal mechanisms of lupus; and basic and clinical studies on understanding the scientific reasons why lupus is more prevalent in women and in minorities, in particular. The NIAMS Task Force on Lupus in High Risk Populations has updated its brochure on "What Black Women Should Know About Lupus" and developed a Community Programs Kit that describes how to develop a lupus awareness program at the community level. The Community Programs booklet provides sample program plans, tips on how to work with the media, and camera-ready materials.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
2. Skin Diseases The House in its report 103-156, page 65, stated: "...Skin diseases affect millions of Americans, necessitating over 60 million doctor visits annually. The Committee is pleased with recent research advances, which have increased scientific knowledge and eased patient suffering. Study of skin diseases has led to progress in cancer therapy, viruses, and gene regulation. The Committee encourages NIAMS to enhance its research efforts in this area."	2. Advances in skin disease research are revealing new information on genetic causes of these diseases as well as providing promising avenues of research on the use of gene therapy in treating skin diseases. The NIAMS will continue to support and encourage basic and clinical research on skin diseases and will fund two additional Research Core Centers for Skin Diseases in FY 1994 for a total of six centers. In addition, as a result of a research announcement, NIAMS will fund new research on chronic wound healing. NIAMS and the National Cancer Institute will support studies to conduct research on educational strategies for the prevention of nonmelanoma and melanoma skin cancers related to exposure to natural and artificial ultraviolet light.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
3. Epidermolysis Bullosa The House in its report 103-156, page 65, stated: "...The Committee remains concerned about research funding for this inherited blistering disease and urges NIAMS to continue an aggressive research program in this area."	3. NIAMS will continue to support a broad portfolio of research on epidermolysis bullosa, including basic molecular research targeted at identifying therapeutic agents. Gene therapy, involving the genetic modification of stem cells of skin in vitro and then transplantation of these to patients, holds promise for the hereditary blistering diseases known as epidermolysis bullosa. NIAMS will participate in an epidermolysis bullosa epidemiology workshop, which will have as a strong focus the analysis of data gathered as part of the epidermolysis bullosa registry.
4. Psoriasis The House in its report 103-156, page 65, stated: "...The Committee is aware that four million Americans are affected by psoriasis and the economic cost of this disease exceeds $1 billion annually. The Committee believes that encouraging innovative basic and clinical research for this disorder should be a high priority for NIAMS."	4. Support for psoriasis research is a high priority within the NIAMS skin diseases research program. The NIAMS currently supports a number of research projects related to the treatment, etiology and genetic regulation of psoriasis. Researchers are examining mechanisms that regulate the growth and differentiation of epidermal cells with the goal of understanding the pathogenesis of skin diseases such as psoriasis and developing effective therapeutic modalities. NIAMS also supports research on the pathogenesis and treatment of psoriasis associated with human immunodeficiency virus (HIV) infection.

NATIONAL INSTITUTES OF HEALTH

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Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
5. Alopecia The House in its report 103-156, page 65, stated: "...The Committee is pleased with the progress made by NIAMS with respect to research on alopecia areata and hopes that the Institute will continue to play a key role in finding a cure for the disease."	5. The NIAMS in collaboration with the National Alopecia Areata Foundation is planning a workshop on advances in alopecia areata research. The Institute will continue to work with the National Alopecia Areata Foundation and the research community to further our understanding of the causes of this disease and the development of effective treatments.
6. Heritable Disorders of Connective Tissue The House in its report 103-156, page 65, stated: "...The Committee is pleased with the support of research on heritable disorders of connective tissue through NIAMS over the past several years and urges the Institute to pursue further development of research in this area."	6. NIAMS, in collaboration with the Coalition for Heritable Connective Tissue Disorders, is planning for the fall of 1994 a workshop to build on recent scientific advances in molecular genetics and molecular biology, and the development of new therapeutics. In response to much interest from the patient and research communities and Congress, NIAMS has issued an invitation seeking applications for the establishment of research registries for rare diseases, including specific heritable disorders of connective tissue and skin diseases, such as the ichthyoses.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
7. Fibromyalgia The House in its report 103-156, page 65, stated: "...The Committee is pleased that NIAMS has recently held a scientific workshop on FMS and urges the Institute to increase its efforts to study this disease."	7. In May 1993, the NIAMS held a highly successful scientific workshop on the current status and future directions of fibromyalgia research, the proceedings of which will be published in the *Journal of Musculoskeletal Pain*. Following the workshop, the Institute issued a Request for Applications (RFA) inviting applications for basic research on the pathogenesis of fibromyalgia. The RFA is intended to promote research that will improve our understanding of the disease and will identify critical processes and mediators of disease that would be used to establish a rational basis for new and effective treatments.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1994 Senate Report	
1. Osteoarthritis The Senate in its report 103-143, page 104, stated: "...While the Committee is aware of the broad range of diseases supported by NIAMS, it is especially concerned about the severity and magnitude of osteoarthritis. The Institute is encouraged to place special emphasis on this degenerative joint disease which causes pain and restricts mobility and is the most widespread of all the arthritic diseases, affecting an estimated 16 million Americans.	1. Expansion of osteoarthritis research is a high priority for NIAMS. In April 1994, NIAMS will sponsor an Osteoarthritis Research workshop to increase the exchange of new scientific information and concepts among an interdisciplinary group of scientists, including orthopaedic surgeons, rheumatologists, epidemiologists, and bioengineers. In September 1994, NIAMS will co-sponsor a Consensus Development Conference on total joint replacement. An October 1993 research announcement will result in research on new orthopaedic biomaterials for the development of improved and longer lasting orthopaedic devices.
The Committee continues to recognize the important contributions made by the specialized centers of research to the national research effort on diseases such as osteoarthritis, osteoporosis, and rheumatoid arthritis. These centers provide an effective means of concentrating research on these high-priority diseases. The Committee is hopeful that the Institute will continue to maintain and adequately fund these centers. In next year's testimony before the Committee, the Institute should be prepared to explain its current and future	NIAMS is pleased with the quality of research supported through its Specialized Centers of Research (SCORs) program, which was established in 1987. The SCOR program is unique, allowing for a multidisciplinary attack on a specific disease, with both basic and clinical research as a requirement. Each research project within a SCOR has high scientific merit and clear research objectives. The SCOR program originated with 9 total centers in three disease areas: rheumatoid arthritis, osteoarthritis, and osteoporosis. The recompetition in 1992 was competitive, and

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
activities to expand the research efforts on osteoarthritis and to provide a progress report on the SCORS.	those ranked as highly meritorious were funded. As a result of the recompetition and new initiatives in lupus, the NIAMS currently supports SCORs for four disease areas: rheumatoid arthritis, osteoarthritis, osteoporosis, and systemic lupus erythematosus.
2. Heritable Disorders of Connective Tissue The Senate in its report 103-143, page 105, stated: "...While the Committee recognizes that this effort has helped bring about impressive scientific discoveries for a few of the heritable disorders of connective tissue, we urge NIAMS and other appropriate institutes within the National Institutes of Health to pursue further development of research in this area. NIAMS is encouraged to sponsor a conference on heritable disorders of connective tissues to follow upon the initiatives which resulted from the 1990 NIAMS-sponsored workshop and to set direction for future research on these conditions which affect more than one-half million Americans."	2. Same response as number 6 in the "1994 House Report."

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
3. Osteoporosis The Senate in its report 103-143, page 105, stated: "... The Committee intends that a significant portion of the increased funding for this Institute be used to expand and intensify the research programs for osteoporosis, Paget's disease, and related bone diseases. The Committee commends NIAMS for providing leadership in this area of research. Because of the Institute's significant efforts, the Committee would like to see bone disease research significantly increased within this Institute as well as in the National Institute on Aging, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute for Dental Research. Although there have been recent advances in osteoporosis, the Committee believes that greater emphasis should be directed toward research on this major women's disease and other related bone diseases."	3. NIAMS has undertaken several major initiatives this year to expand research on osteoporosis. A Federal Working Group on Bone Disorders has been established under the auspices of the Arthritis and Musculoskeletal Diseases Interagency Coordinating Committee. The first meeting was held on February 9, 1994. To expand basic and clinical research on osteoporosis and related bone disorders, NIAMS launched its new BONES (Basic Research on Osteoporosis: New Experimental Strategies) initiative that includes a Request for Applications (RFA) inviting new research on: growth factors and other regulators of bone metabolism; the role of genetics in bone growth and remodeling; effects of estrogens and androgens on bone metabolism; biomarkers; and bone architecture and fragility. A Consensus Development Conference that will consider the influence of calcium on osteoporosis, breast and colon cancers, and hypertension is planned for June 1994. A major objective of the conference is to establish optimum levels of calcium intake for all age levels. In September, NIAMS will award a grant to support a Resource Center on Osteoporosis, Paget's Disease and Related Bone Disorders.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
4. Fibromyalgia The Senate in its report 103-143, page 106, stated: "...The Committee believes the NIAMS should aggressively pursue stimulating increased interest in both basic and clinical research on FMS and has provided sufficient funds to significantly increase support for this important research, most notably neuroendocrine abnormalities."	4. Same response as number 7 in "1994 House Report."
5. Rheumatoid Arthritis The Senate in its report 103-143, page 106, stated: "...The Committee is very concerned that there remains the question whether rheumatoid arthritis can be relieved or cured through the intravenous administration of antibiotics. The Committee allocation includes the same level of funding provided last year for this and related research activities. Therefore, the Committee directs the NIAMS, within the funds provided, to initiate a pilot clinical trial to study the efficacy of intravenous antibiotic therapy in treating rheumatoid arthritis. This study should include measures of disease activity and, pending the outcome, be considered the initial step in developing a multicenter clinical trial."	5. The results of the Minocycline in Rheumatoid Arthritis Trial (MIRA) were reported at the November 7, 1993, Annual Scientific Meeting of the American College of Rheumatology. Results show that minocycline has some benefit for treating rheumatoid arthritis; how effective minocycline is compared to other treatments for rheumatoid arthritis remains to be determined. Full details of the trial will be available following publication of the results in a peer-reviewed journal. As requested, NIAMS will initiate a pilot clinical trial to study the efficacy of intravenous antibiotic therapy in treating rheumatoid arthritis.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
6. Paget's Disease The Senate in its report 103-143, page 129, stated: "...The Committee has been pleased with the collaborative efforts demonstrated by various Institutes to address aspects of Paget's disease. These initiatives should be continued and expanded, particularly within ongoing NIH center and laboratory programs.	6. NIAMS the lead institute for research on Paget's disease will continue to support and encourage research applications that relate to Paget's disease of bone and related disorders. The newly established Federal Working Group on Bone Disorders will provide an ideal forum for collaborative research efforts across NIH and other Federal agencies with interest in this disease.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation......	Section 301	42§241	Indefinite	>$213,115,000	Indefinite	>$220,828,000
National Institute of Arthritis and Musculoskeletal and Skin Diseases.................	Title IV	42§285d 1-7	Indefinite		Indefinite	
National Research Service Awards	Title IV Part G	42§288	$400,000,000	7,370,000	Such sums as necessary	7,585,000
Total Budget Authority....				220,485,000		228,413,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	$106,733,000	$140,225,000	$129,475,000	$138,713,000
1988	132,089,000	154,632,000	153,867,000	147,679,000
1989	158,244,000 2/	155,487,000 2/	161,244,000 2/	159,897,000 3/
1990	167,334,000 4/	171,673,000	171,688,000	171,250,000 5/
1990 Sequester				-2,320,000
1991	176,080,000	191,397,000 6/	198,746,000	193,247,000 7/
1991 Sequester				-3,000
1992	204,797,000	204,977,000	203,076,000	203,047,000 8/
1993	214,929,000	214,619,000	214,619,000	212,456,000 9/
1994	210,382,000	223,280,000	223,280,000	223,280,000
1995	228,413,000 10/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for AIDS research and education ($687,000).
3/ Excludes funds for AIDS research and education ($673,000), for Gramm-Rudman-Hollings spending targets ($1,943,000), and for the FY 1989 Procurement Reform Reduction ($91,000).
4/ The 1990 request excludes funds for the National HIV program ($1,254,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
5/ Excludes enacted administrative reductions of $431,000.
6/ Excludes funds for NRSA training, which is unauthorized.
7/ Excludes enacted administrative reductions of $5,195,000.
8/ Excludes enacted administrative reductions of $1,089,000.
9/ Excludes enacted administrative reductions ($1,717,000), Salaries and Expenses reductions ($441,000), Consultant Services reductions ($5,000).
10/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

BUDGET AUTHORITY BY ACTIVITY
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Changes	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Arthritis and musculoskeletal and skin diseases........		$168,655		$177,138		$183,357		$193,121		$200,558		$7,437
Intramural research....	70	14,332	85	15,171	82	17,259	77	17,566	77	17,830	0	264
Research management and support..........	70	8,829	82	9,513	84	9,832	73	9,798	73	10,025	0	227
Subtotal, obligations	140	191,816	167	201,822	166	210,448	150	220,485	150	228,413	0	7,928
Unobligated balance lapsing..............		17		31		39		---		---		
Total, Budget Authority	140	191,833	167	201,853	166	210,487	150	220,485	150	228,413	0	7,928

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH office of AIDS Research.

Justification

National Institute of Arthritis and Musculoskeletal and Skin Diseases

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
166	$210,487,000	150	$220,485,000	150	$228,413,000	0	+$7,928,000

General Statement

This document provides justification for the FY 1995 Non-Aids activities of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

Arthritis and musculoskeletal and skin diseases are the most common causes of pain, disability, and disfigurement in the United States today. These diseases in the aggregate will afflict almost every American at some time in their lives. Moreover, the immense problems associated with these diseases will increase significantly as more Americans live longer. The quest to find preventions, treatments, and cures for these diseases and the suffering they impose represents the enormous challenges facing the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

The NIAMS has a broad, diverse, and substantive mandate to address and combat such devastating diseases as rheumatoid arthritis, osteoporosis, osteoarthritis, lupus, osteogenesis imperfecta, epidermolysis bullosa, severe psoriasis, and scleroderma. Some of these diseases affect people of all ages, races, and gender, whereas others disproportionately affect special populations, such as women, minorities, children, athletes, and the elderly. The Institute is dedicated to launching innovative research approaches to provide new insights into the causes and treatments of these diseases.

Osteoporosis and osteoarthritis, both common and disabling diseases of the elderly, will take an escalating toll on our nation as the age profile of our society changes. The NIAMS is committed to reducing significantly the physical infirmity, impaired quality of life, and economic costs that result from these diseases. At the same time, the Institute is dedicated to meeting the special needs of younger people by supporting research in the various forms of arthritis in children, sports injuries, and devastating hereditary skin and connective tissue diseases, such as osteogenesis imperfecta--"brittle bone" disease, epidermolysis bullosa, Marfan's syndrome, and muscular dystrophy.

Research on diseases that disproportionately affect women and minorities, such as lupus, a disease to which African American women are especially prone, and scleroderma, a life-threatening disease that often affects women in their childbearing years, will continue to be very prominent in the research agenda of NIAMS as the Institute confronts the challenges of the future.

The pursuit of basic science is critical to addressing the missions of NIAMS. One of the most significant advances in basic research this year occurred in the field of muscle biology in studies employing high-powered x-ray crystallography. In the culmination of a 10-year effort, researchers have discovered the three-dimensional structure of myosin, the major muscle protein without which humans could not move or breathe. By combining this new information on myosin with new data from electron microscopy, the researchers developed a new structural model of how chemical energy gets changed into movement. These studies have revealed with precision how the molecules in muscle use energy to produce force and motion.

Osteoporosis--the major underlying cause of bone fractures in postmenopausal women and the elderly--is an eminently preventable disease. Basic research is providing increased understanding of factors responsible for maintaining healthy bone--knowledge critical for understanding and preventing osteoporosis, as well as Paget's disease and other bone disorders. This year, for the first time, investigators have identified the primitive cells in the bone marrow that give rise to osteoclasts, bone cells that cause bone to be broken down and resorbed. Other research has uncovered how certain genes govern bone cells and regulate bone turnover.

Clinical advances in osteoporosis research are also moving us further in the direction of prevention. Increases in bone mass, which are promoted by high calcium intake and physical activity, have been found to continue into the third decade of life in healthy young women. Building greater bone mass in young women may lessen the risk of osteoporosis later on. Investigators have also developed a new urine test as an accurate, sensitive marker of bone resorption. Researchers are also exploring the role of reproductive risk and protective factors for osteoporosis, such as number of children and length of time from menarche to menopause, so that appropriate intervention strategies can be targeted to those at high risk. NIAMS will continue to fund clinical trials of preventive interventions for preserving bone mass in women during the postmenopausal period.

An exciting new avenue of research in lupus indicates that the cause of this disease may involve defects in a process called apoptosis by which the body eliminates unnecessary, damaged, or potentially harmful cells. If the process of apoptosis is defective, cells with the potential to react against the body's own tissues will survive and can, in this way, result in autoimmune diseases, such as lupus. In mouse models of lupus, researchers have identified and replaced the flawed gene believed to cause this defect in apoptosis, and as a promising new advance, the mice no longer develop signs of lupus. Greater understanding of the role of apoptosis in lupus may lead to new, targeted treatments for this disease.

Recent research on rheumatoid arthritis has revealed that improvement of the arthritis during pregnancy is related to how much a mother and unborn child differ genetically. Rheumatoid arthritis improved in three-fourths of pregnancies studied. Researchers now believe that genetic differences between the mother and child may set off maternal immune responses that modify the disease process. These findings provide an intriguing new focus for uncovering causes of remission in rheumatoid arthritis. Future research in this area may yield new treatment strategies for this inflammatory disease of the joints.

In other research on rheumatoid arthritis, a recent clinical trial conducted at multiple sites demonstrated that the drug minocycline--which has been advocated as an effective treatment for rheumatoid arthritis--has been shown to have some benefit in treating the arthritis.

In a ground-breaking study on the causes of spinal arthritis, researchers have now proven in an animal model of the disease that the presence of an infectious agent and genetic susceptibility are both necessary for the disease to occur. The discovery is the culmination of a remarkable research effort that began with a study to determine if a human gene called HLA-B27 was the major cause of spinal arthritis. In this earlier study, researchers determined that rats fertilized with the human HLA-B27 gene, found in over 90 percent of patients with spinal arthritis, developed almost all the human symptoms of spinal arthritis, plus skin lesions similar to psoriasis and Reiter's disease. In the follow-up study, researchers repeated the experiment using HLA-B27 rats bred in a completely germ-free environment. This time the rats developed the skin changes associated with psoriasis and Reiter's disease. However, they did not develop the joint or bowel inflammation seen in animals exposed to common germs in a normal environment. The discovery shows that the human HLA-B27 gene alone can cause the skin disorder, but an infectious agent must also be present to develop the arthritis. Future research seeks to identify the responsible infectious agent and may include the development of an intervention that would block the link between the gene and the infectious agent, thereby preventing the arthritis from occurring. The research also provides important new data on the causes of psoriasis.

In a recent study of osteoarthritis, researchers have determined that certain "antibiotics" may be useful in the treatment of the arthritis for reasons other than their ability to inhibit infection. In this experiment, doxycycline, an antibiotic with other biologic actions, was given to animals with damaged knee joints immediately after surgery. Animals who had received the drug either did not develop osteoarthritis, or developed a mild form of the disease. Animals not given the doxycycline developed the cartilage damage of osteoarthritis. There was no evidence of infection in the animal model. The benefit of doxycycline was ascribed to its ability to inhibit collagenase, an enzyme that degrades a major component of cartilage, rather than its ability to eradicate infection.

In an important step in the fight against muscular dystrophy, researchers have discovered a gene therapy technique that prevents mice from developing a condition similar to Duchenne muscular dystrophy (DMD), the most common form of childhood muscular dystrophy. By inserting a normal gene for the protein dystrophin into mice that lacked a functioning form of the gene, researchers were able to correct the defect that causes the muscle degeneration associated with muscular dystrophy. These findings suggest that, in the future, gene therapy for humans with DMD may be feasible.

An estimated 60 million Americans suffer from skin diseases that require a visit to a physician at least once a year. Exciting advances at the molecular level are providing insights into the underlying causes of many of these diseases, bringing us closer to treatments aimed at remedying these defects. Recent research suggests two hypotheses as to why the fibrils that normally link the outer layer of the skin to the inner layer are missing in the dystrophic form of epidermolysis bullosa (EB), a set of devastating blistering diseases. Future studies will determine which of these hypotheses is correct. In another form of EB (EB simplex), caused by defects in structural proteins of skin called keratins, it has been shown that there is a correlation between the specific type of genetic defect and disease severity. Similar discoveries have been achieved by both our intramural and extramural scientists for epidermolytic hyperkeratosis, a scaling skin disorder whose genetic basis was recently discovered.

Each such breakthrough that is uncovered by researchers supported by NIAMS moves us closer to preventing and curing some of the most crippling and costly diseases that affect our Nation. With this in mind, the NIAMS is eager to continue to foster and support research that could potentially lead to improved lives for millions of Americans.

Purpose and Method of Operation

Extramural research and training are supported through five program areas: arthritis, bone biology and bone diseases, musculoskeletal diseases, muscle biology, and skin diseases. Funding mechanisms include research project grants, research centers, other research grants, research training, and research and development contracts. Intramural research is conducted at three research laboratories and one clinical research branch. The leadership and scientific direction of the Institute are funded through the activity entitled Research Management and Support.

The President's appropriation request of $228,413,000 for this account represents current law requirements. No proposed law amounts are included.

Funding for the National Institute of Arthritis and Musculoskeletal and Skin Diseases during the last five years has been as follows:

	Amount	FTE
FY 1990	$167,325,000	121
FY 1991	191,833,000	140
FY 1992	201,853,000	167
FY 1993	210,487,000	166
FY 1994	220,485,000	150

Overall Budget Policy

The FY 1995 budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases is $228,413,000, an increase of $7,928,000 over the comparable FY 1994 level of $220,485,000. The request includes 150 FTEs, the same level as FY 1994. At the FY 1995 request level, the Institute will support 488 noncompeting research project grants at a level of $111,089,000 and 193 competing grants at a level of $41,377,000 compared to 506 and 174, respectively in FY 1994. The FY 1995 request includes $27,008,000 for 30 research centers, $7,854,000 for other research, $7,585,000 for research training, and $4,817,000 for R&D contracts. Intramural research will be conducted at a level of $17,830,000 compared with $17,566,000 in FY 1994. Research management and support activities will be funded at a level of $10,025,000 compared to $9,798,000 in FY 1994.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Extramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$183,357,000	$193,121,000	$200,558,000	+$7,437,000

The NIAMS has primary responsibility at the National Institutes of Health for extramural research and research training in arthritis, bone biology and bone diseases, musculoskeletal diseases, muscle biology, and skin diseases.

Funding for the Arthritis and Musculoskeletal and Skin Diseases Program during the last five years has been as follows:

	Amount
FY 1990	$148,134,000
FY 1991	168,655,000
FY 1992	177,169,000
FY 1993	183,357,000
FY 1994	193,121,000

Rationale for the Budget Request

With the FY 1995 extramural request these funds will provide support for the following activity: Arthritis and Musculoskeletal and Skin Diseases Program, $200,558,000, an increase of $7,437,000 or 3.85 percent over the FY 1994 estimate of $193,121,000. Following are selected examples of current research activities and plans for FY 1995 based on the request level:

Arthritis and Musculoskeletal and Skin Diseases

Rheumatoid Arthritis -- Research continues to yield clues on the role of the immune system in causing rheumatoid arthritis, a chronic inflammatory disease that affects more than two million Americans (predominantly women). Scientists previously uncovered a promising piece of the puzzle when they successfully vaccinated healthy rats against arthritis with a preparation of white blood cells obtained from a separate group of rats suffering from arthritis. Investigators are now carrying this work forward by isolating and characterizing small protein fragments of the white blood cells for use in eliciting immunity. This research has the potential to lead to a vaccine for protecting humans from rheumatoid arthritis.

To exploit the recent finding that genetic differences between mother and unborn child can set off a beneficial immune response in the mother during pregnancy, NIAMS investigators are carrying out basic research on proteins known as genetic markers, which are located on the surfaces of most cells in the body, to better understand the immune system's response to them. Scientists are also investigating the mechanisms by which white blood cells invade the joint tissues of patients with rheumatoid arthritis. Developing a more complete understanding of this process should provide clues concerning means to prevent or control joint inflammation.

Arthritis in Children -- This year, the NIAMS held a highly productive scientific workshop on basic and clinical research for the several rheumatic diseases of children. After its publication, the Institute will encourage broadly new research, as recommended by leaders in the field. Also this year, the NIAMS funded an Exploratory Research Center in Juvenile Rheumatic Diseases. Scientists at this center will investigate the genetic basis, causes of inflammation, and the role of bacteria and viruses as triggers of these diseases that affect more than 200,000 children, from toddlers to teenagers. Almost half of the children who suffer from these rheumatic diseases will carry serious disabilities into adulthood, including crippling limbs and severe complications, and some may even experience premature death. At present, in this country, too small a number of researchers specialize in juvenile arthritis. Accordingly, the Institute will continue to encourage the recruitment of pediatric rheumatologists and other scientists to this important field of study.

Osteoarthritis -- An estimated 16 million Americans suffer from osteoarthritis, the most common of all the rheumatic diseases. This disease, which destroys the cartilage of joints, leads to millions of doctor's office visits and lost workdays each year. With the ultimate aim of lessening this burden, scientists have been working to develop biochemical markers to detect and measure joint degeneration over time. Some markers for following the progression of osteoarthritis during its later stages have already been discovered. Next steps will involve improving the accuracy of these markers and developing new markers capable of detecting osteoarthritis in its early stages. Earlier detection of the disease would facilitate intervention, such as lessening impact loading on joints, before irreversible damage occurs.

NIAMS scientists are also investigating the enzyme collagenase, which destroys cartilage and other joint tissues. They have developed inhibitors of collagenase that have potential as novel anti-arthritic drugs. Other NIAMS scientists are pursuing a different approach by suppressing collagenase production through genetic manipulations. To learn more about the specific causes of osteoarthritis, NIAMS will continue to study the disease in the Pima Indians of Arizona--a unique population that is especially prone to developing osteoarthritis.

Osteoporosis -- In a landmark discovery, researchers have recently found a gene (for the vitamin D receptor) that may be able to identify, early in life, individuals at high risk for osteoporosis. Osteoporosis currently affects more than 26 million Americans, 20 million of whom are women, and costs the Nation over $10 billion each year. The disease usually results from two factors: the deficient development of the peak bone strength (density) attained in early life, and excessive rates of bone loss in later life. Until now, genes responsible for bone density have not been identified. The new findings need to be extended to provide possible explanations for the variation in bone density among both individuals and ethnic groups. Further research is also needed to uncover the precise role of vitamin D in bone formation and metabolism. These investigations could pave the way for developing new targeted approaches to preventing and treating osteoporosis.

To stimulate other research on osteoporosis, NIAMS has developed the BONES (Basic Research on Osteoporosis: New Experimental Strategies) initiative. This initiative will promote new research to expand the knowledge base for the development of new therapeutic strategies for osteoporosis. In mounting the BONES initiative, NIAMS will invite new applications for research in the basic areas of bone structure, formation, remodeling, and repair. This new research on osteoporosis is likely to lead to a broader range of prevention strategies and therapies with which to combat one of the country's most chronic and disabling diseases.

The importance of calcium intake in attaining adult peak bone mass has been well established, and recent studies indicate that calcium plays a role in reducing hypertension and colon cancer as well. Subsequent research will focus on determining calcium intakes that are optimal for developing and maintaining strong bones. The Institute also plans to implement a public awareness campaign to better inform the public about these and other prevention strategies for osteoporosis.

Systemic Lupus Erythematosus -- In patients with lupus the body produces abnormal antibodies that react against the individual's own tissues. In FY 1993 the Institute funded a group of new research projects to study factors that cause women, especially African American women, to have a higher prevalence of lupus than men; and two new specialized centers of research on lupus, fostering a full range of investigation from basic to clinical. To better understand why the immune system goes awry in patients with lupus, researchers are tackling the issue on several fronts: identification of factors that cause injury in the kidneys, brain, skin, and other affected organs; development of new systems to study the abnormal antibodies in lupus patients; elucidation of genetic factors underlying autoimmunity; and characterization of environmental factors in induction or exacerbation of disease.

The Institute anticipates enhancing and broadening its public information campaign on lupus to inform young African American women of the symptoms of lupus and to encourage them to seek medical care when such symptoms appear. For physicians and other health professionals, the Institute will also develop a continuing education program on the diagnosis and treatment of lupus.

Scleroderma -- Scleroderma is a devastating, sometimes fatal disease that affects primarily women in midlife. The disease is characterized by excessive accumulation of the connective tissue protein collagen in the skin, causing it to harden, and by the narrowing of small blood vessels. When this narrowing occurs in vital organs such as the heart, lungs, and kidneys, there can be life-threatening consequences. Recent advances in basic research in the molecular biology of connective tissue and in immunology have created many exciting opportunities to advance the field of scleroderma research. In addition, scientists have developed two mouse models of scleroderma that will allow the identification of genes that regulate abnormal collagen deposition and the initiation of vascular and tissue injury.

Fibromyalgia -- Fibromyalgia is a disorder that causes widespread pain and tenderness throughout soft tissues such as muscles and tendons. The disease is associated with chronic aching, tender points, and sleep disturbances. During the past year, NIAMS sponsored a national conference to determine the current status and future directions of research on fibromyalgia. To foster new knowledge concerning fibromyalgia, the Institute has issued a Request for Applications for basic research on the causal mechanisms of this disease. The goal in supporting such research is to identify critical processes and mediators of disease that could be used to establish new and effective treatments.

Heritable Connective Tissue Disorders -- Connective tissue is diffusely distributed throughout the body; it is the principal component of cartilage, tendons, ligaments, skin, and membranes that hold internal organs together and in place. Much has been learned about the composition of connective tissue in its various specialized forms. Much more remains to be learned about the hereditary factors that control the synthesis and metabolism of this vital and ubiquitous tissue. Osteogenesis imperfecta, Ehlers-Danlos syndrome, and Marfan syndrome are but a few of the hereditary connective tissue diseases that are caused by specific genetic defects and passed from one generation to the next. NIAMS investigators will be carrying out research on these and other heritable connective tissue diseases to understand better the relationships between defective genes and specific clinical manifestations of disease. The Institute is also working with the NIH Office of Rare Diseases to establish a database and monitoring system to enhance and support research on these heritable connective tissue disorders.

Musculoskeletal Diseases -- Musculoskeletal diseases have a substantial impact on health and quality of life, as well as on the use of health care resources. NIAMS investigators are studying ways to improve musculoskeletal function in people with disabilities. The Institute has initiated the Program of Excellence in Orthopaedic Biomaterials which will result in new research on better and longer-lasting artificial joints. Together with the NIH Office of Medical Applications of Research, the Institute is planning a consensus development conference on total joint replacements to discuss and disseminate information to medical practitioners concerning the latest biomaterials and procedures for artificial joints. Orthopaedic implants, such as total knee and hip replacements, are used in the treatment of osteoarthritis, rheumatoid arthritis, lupus, and other disorders. Some 5 million people in the United States currently have such orthopaedic devices implanted.

Workers employed in many diverse segments of industry (computer terminal operators, cashiers, meat cutters, etc.) suffer from repetitive motion injuries--such as the carpal tunnel syndrome--in many parts of the body. These injuries are common and costly medical problems. Because the mechanisms that cause repetitive motion injury are not well understood, the Institute--along with the National Institute of Child Health and Human Development and the National Institute of Occupational Safety and Health--is convening experts in this field to formulate future research directions for repetitive motion syndromes.

Ichthyosis -- Ichthyosis comprises a family of genetic disorders characterized by dry, thickened, scaling skin. Last year, NIAMS researchers found the gene responsible for one form of ichthyosis. Investigators are now studying relationships among the different forms of this inherited condition. To facilitate identification of the molecular basis of various rare diseases, improve techniques of diagnosis, and develop more effective methods for treatment and prevention, NIAMS plans to establish several small patient registries. These will provide researchers access to families with uncommon skin problems, such as ichthyosis, and to families with rare hereditary connective tissue disorders, such as Marfan's syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome, as well as rare rheumatic diseases, such as scleroderma.

Alopecia Areata -- Alopecia areata is a disease of the hair follicle causing local baldness or complete loss of hair. The psychological impact of this disorder can be debilitating. NIAMS staff are currently working with members of the National Alopecia Areata Foundation to sponsor a new research workshop on alopecia areata intended to provide for exchange of information among scientists and to stimulate more research on the disease. Research opportunities include studies on causes of alopecia areata, as well as investigations into factors controlling hair growth.

Wound Healing -- Scientists are making significant progress in dissecting the complex sequence of events that allows traumatized tissue to heal itself. Thus far, researchers have identified several growth factors, specialized molecules that exert their actions during different stages of wound healing. Wounds that fail to heal remain a major problem and health concern, particularly in the elderly who suffer greatly from bedsores. NIAMS, together with other Institutes, is actively encouraging new research in this area.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Intramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	
82	$17,298,000	77	$17,566,000	77	$17,830,000	0	+$264,0

The primary purposes of the Intramural Research Program of the NIAMS ar to develop new knowledge in human biology and make major discoveries with which to address the health problems within the Institute's missions. These include a wide range of investigations, from the most basic laboratory research to clinical trials evaluating new therapies, as well as training ar career development of junior scientists. The intramural program enables researchers to take advantage of special features that are available at the NIH, including the extensive variety of scientific expertise that facilitate collaboration among diverse investigators, and the ability to closely integrate laboratory and clinical research.

Four major units carry out the research conducted within the NIAMS Intramural Research Program. These include the Arthritis and Rheumatism Branch, the Laboratory of Physical Biology, the Laboratory of Structural Biology Research, and the Laboratory of Skin Biology.

Funding for the Intramural Research Program during the last five years has been as follows:

	Amount	FTE
FY 1990	$11,933,000	57
FY 1991	14,349,000	70
FY 1992	15,171,000	85
FY 1993	17,298,000	82
FY 1994	17,566,000	77

Rationale for the Budget Request

The FY 1995 budget request for the Intramural Research Program is $17,830,000, an increase of $264,000 over the FY 1994 estimate of $17,566,00 The following outlines some of the ongoing research activities and future research directions of the NIAMS Intramural Research Program:

Rheumatoid Arthritis -- In previous studies with animals, intramural scientists showed that development of rheumatoid arthritis involves defects the complex nervous system-hormone (neuroendocrine) network that controls th body's response to inflammatory stimuli and other stresses. They have now found a hormone that may carry signals between the neuroendocrine and inflammatory systems in humans suffering from rheumatoid arthritis. The researchers are comparing neuroendocrine responses in rheumatoid arthritis patients and normal individuals in hopes of demonstrating that abnormal interactions among the nervous, immune, and hormone systems predispose individuals to disease. If this hypothesis is proved, it could lead to development of innovative new preventive strategies.

Systemic Lupus Erythematosus -- Over the years intramural scientists have conducted several long-term clinical trials using selected immunosuppressive drugs in the treatment of lupus nephritis--a kidney disease that can be life-threatening. To circumvent the toxicity associated with immunosuppressive drugs, these scientists are now exploring the use of biological agents, created through sophisticated laboratory techniques. A promising pilot study in patients treated with one such agent, a monoclonal antibody, showed reduced inflammation and led to clinical improvement.

Origins of Autoimmune Diseases -- Intramural scientists are studying the origins of autoimmune diseases (in which the body attacks its own tissues), the abnormal and destructive antibodies found in these diseases, and the possibility that viruses play a role in their onset. Polymyositis, an autoimmune disease in which muscle becomes inflamed and weakened, is the object of concerted research because study of its unique disease-specific antibodies could unravel the complex interplay between various elements (immune, genetic, environmental, etc.) that set off autoimmune diseases. NIAMS investigators are developing a mouse model of polymyositis that could make it possible to determine whether viruses play a role in the onset of this disease and, by implication, the onset of more common autoimmune disorders such as rheumatoid arthritis, lupus, and scleroderma.

Chemical Immunology -- One of the more important antibodies in the immune system is immunoglobulin E (IgE). Binding of IgE to receptors found on the surface of connective tissue cells throughout the body plays a key role in triggering inflammation and allergic reactions. Intramural scientists are investigating the structure and function of receptors for IgE through a variety of approaches, including sophisticated cell culture and genetic techniques to define the critical regions where IgE binding takes place. This could lead to development of means to block the binding of IgE to its receptor, thereby preventing allergic and inflammatory reactions. Additionally, the IgE receptor-antibody linkage could serve as a paradigm for the study of other receptor-antibody interactions.

Hereditary Skin Diseases -- Genetic studies of hereditary skin disorders are aimed at finding the specific gene defect in a variety of skin diseases. In the past year, NIAMS researchers identified a gene abnormality in more than a dozen families with a particular type of the scaling skin disease ichthyosis. Because there appears to be a correlation between the clinical signs and symptoms of the disorder and the specific gene mutation involved, the investigators have proposed a classification system for the disease based on its clinical presentation. This will pave the way for genetic counseling and prenatal diagnosis.

Structural Biology -- Using high-resolution electron microscopy and computer imaging, intramural scientists are investigating the structure of viruses and virus-related particles, including the surface of the AIDS virus. This research is providing knowledge about the receptor-recognition proteins on the surface of infectious agents, which serve as a link with the body's immune system. These fundamental investigations could provide insight not only into AIDS, but also into other diseases in which infectious agents play role.

Crystallography Studies -- In December 1992 a crystallography unit was initiated to study large, biologically important molecules, including comple enzymes involved in autoimmune reactions. During the past year, scientists i this new unit purified an enzyme known to be a target of the autoimmune response in patients with polymyositis. Working cooperatively with NIAMS physician-scientists who are studying this inflammatory muscle disease, the investigators obtained crystals of the enzyme large enough for study by complex biophysical procedures. This first step will enable them to view--a the molecular level--the complex interaction between autoantibody and target enzyme. A clearer view of this interaction could markedly enhance knowledge of the origins and development of polymyositis. More important, it could le to greater knowledge of the underlying factors in more common autoimmune disorders.

Rehabilitation/Biomechanics -- In collaboration with the Department of Rehabilitation Medicine at the NIH Clinical Center, the NIAMS Intramural Research Program supports research in biomechanics aimed at enhancing the mobility of patients with severe arthritic conditions. Scientists are studying the movement of mechanical energy through the ankle and knee preoperatively and postoperatively to measure improvement following foot surgery and to design better artificial limbs and footwear. Other studies a focusing on the various biomechanical causes of falls, such as slips and trips, to minimize risk factors. Prevention of falls, along with consequent hip fractures, could result in tremendous economic savings in addition to improving the quality of life for the Nation's older citizens.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Research Management and Support

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
84	$9,832,000	73	$9,798,000	73	$10,025,000	0	+$227,000

The Research Management and Support (RMS) activity provides the staff and resources necessary to support the overall administration and coordination of the managerial and scientific programs of the Institute. Staff included in RMS provide direction for scientific programs, evaluate research needs, develop program announcements, manage the review and award of grant and contract applications, and support and monitor funded research projects. RMS also supports staff to manage and direct equal employment opportunity issues. Other principal functions under this activity include planning, policy development, financial management, personnel management, information dissemination, data processing, procurement, and property management.

Funding for the Research Management and Support activity during the last five years has been as follows:

	Amount	FTE
FY 1990	$7,258,000	64
FY 1991	8,829,000	70
FY 1992	9,513,000	82
FY 1993	9,832,000	84
FY 1994	9,798,000	73

Rationale for the Budget Request

The FY 1995 budget request for Research Management and Support is $10,025,000, an increase of $227,000 or 2.3 percent over the FY 1994 estimate of $9,798,000.

These funds will be used to support the Office of the Director and the Extramural Program. The Office of the Director provides the guidance and professional leadership needed to manage the Institute. Within the Office of the Director are the various administrative management offices which provide advice to the Director and his staff, and direct the administrative functions of the Institute. The Extramural Program comprises the professional and support personnel who are responsible for administration of the Institute's grant and contract activities.

Also supported by the RMS activity are the Office of Scientific and Health Communications which serves as the focal point for most of the public information campaigns; the Office of Disease Prevention, Epidemiology, and Clinical Applications; and the Office of Program Planning and Evaluation.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

1995 Congressional Justification

Detail of Full-time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	46	37	37
Extramural Program	38	36	36
Intramural Research	82	77	77
Total	166	150	150

Average GS/GM Grade

1990	9.5
1991	10.1
1992	9.6
1993	10.5
1994	10.5
1995	10.5

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

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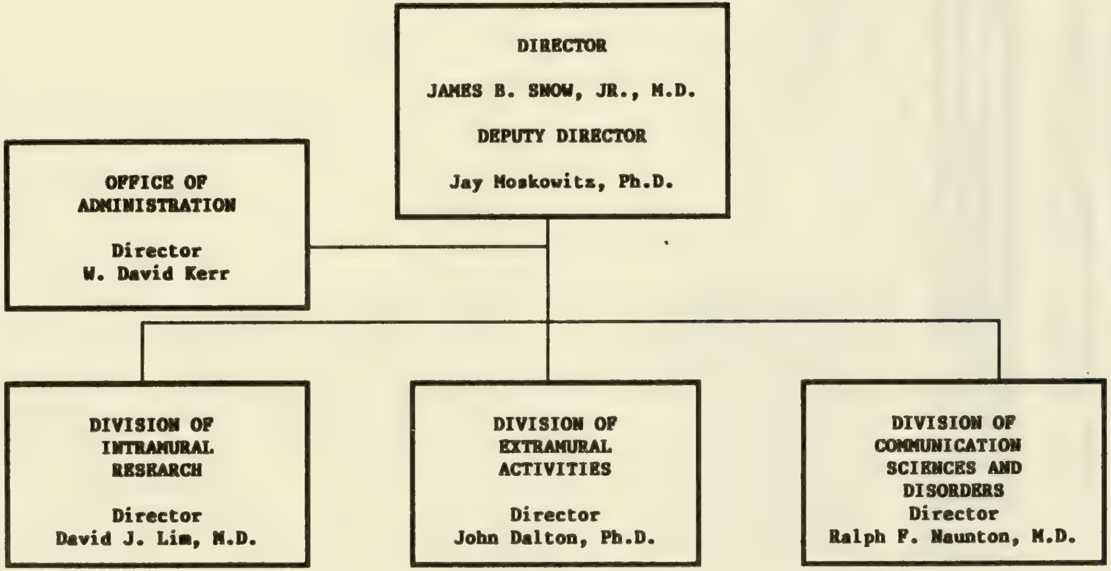
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL INSTITUTE ON DEAFNESS AND
OTHER COMMUNICATION DISORDERS



NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

For carrying out section 301 and title IV of the Public Health Service Act with respect to deafness and other communication disorders, [$162,823,000] *$167,129,000 of which $1,766,000 shall not become available for obligation until September 19, 1995*. (Department of Health and Human Services Appropriation Act, 1994.)

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NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Language Analysis

Language Provision	Explanation
"....of which $1,766,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation..................	$156,342,000	$162,823,000	$167,129,000
Section 513 S&E reduction.......	-264,000	---	---
Section 511 reduction...........	-1,251,000	---	---
Section 513 reduction...........	-13,000	---	---
Subtotal, adjusted appropriation...........	154,814,000	162,823,000	167,129,000
Real transfer to: Other NIH Account for Tuberculosis Research.......	-38,000	---	---
Comparable transfer to: Office of AIDS Research for HIV activities..............	-618,000	-1,507,000	---
Subtotal, adjusted budget authority................	154,158,000	161,316,000	167,129,000
Unobligated balance, lapsing....	-121,000	---	---
Total obligations.............	154,037,000	161,316,000	167,129,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1993 - $2,022,000; FY 1994 - $2,500,000; FY 1995 - $2,500,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research projects:						
Noncompeting	366	$80,851,000	381	$81,566,000	355	$82,182,000
Administrative supplementals	(8)	235,000	(10)	250,000	(10)	266,000
Competing projects:						
Renewals	53	13,741,000	53	15,620,000	58	17,619,000
New	76	11,170,000	77	12,734,000	83	14,322,000
Supplements	1	35,000	1	86,000	1	45,000
Subtotal, competing	130	24,946,000	131	28,440,000	142	31,986,000
Subtotal, research projects	496	106,032,000	512	110,256,000	497	114,434,000
Research Centers:						
Specialized/comprehensive centers	15	16,581,000	16	17,601,000	16	18,152,000
Other Research:						
Research career programs	42	3,285,000	44	3,686,000	44	3,789,000
Cooperative clinical	1	1,154,000	1	1,283,000	1	1,319,000
Minority biomedical support	0	320,000	0	530,000	0	575,000
Other research	51	2,252,000	57	2,035,000	57	2,125,000
Subtotal, other research	94	7,011,000	102	7,534,000	102	7,808,000
Total, research grants	605	129,624,000	630	135,391,000	615	140,394,000

Research Training:						
Individual awards:						
Noncompeting	19	499,000	23	621,000	32	952,000
Competing awards	16	366,000	13	321,000	4	77,000
Subtotal, individual	35	865,000	36	942,000	36	1,029,000
Institutional awards:						
Noncompeting	136	3,517,000	133	3,791,000	139	4,026,000
Competing awards	18	452,000	16	411,000	10	293,000
Subtotal, institutional	154	3,969,000	149	4,202,000	149	4,319,000
Total, research training	189	4,834,000	185	5,144,000	185	5,348,000
Research and development contracts	12	3,855,000	17	5,741,000	17	5,964,000
	FTEs		FTEs		FTEs	
Intramural research	44	9,223,000	43	9,304,000	43	9,459,000
Research management and support	89	7,240,000	74	7,243,000	74	7,524,000
Total	133	154,776,000	117	162,823,000	117	168,689,000
Clinical trials		(5,432,000)		(5,717,000)		(5,919,000)

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Summary of Changes

1994 Estimated budget authority..................................	$161,316,000
1995 Estimated budget authority..................................	167,129,000
Net Change..	+5,813,000

	1994 Current Estimate Base (FTEs)	1994 Current Estimate Base Budget Authority	Change from Base (FTEs)	Change from Base Budget Authority
Changes:				
A. Built-in:				
1. Intramural:				
a. Within grade increase....	---	$3,687,000	---	+42,000
b. One less day of pay......	---	3,687,000	---	-14,000
c. Annualization of January 1994 pay increases.....	---	3,687,000	---	+30,000
d. 1995 pay increases.......	---	3,687,000	---	+50,000
e. Unemployment compensation	---	3,687,000	---	+2,000
f. FTS rate increases.......	---	3,687,000	---	+1,000
g. Payment for centrally furnished services.....	---	1,076,000	---	+44,000
h. Increased cost of service and supply fund	---	452,000	---	+25,000
i. Increased cost of materials and other supplies...............	---	4,089,000	---	+102,000
Subtotal.................				+282,000
2. Research Management & Support:				
a. Within grade increase....	---	$ 4,497,000	---	+61,000
b. One less day of pay......	---	4,497,000	---	-17,000
c. Annualization of January 1994 pay increases.....	---	4,497,000	---	+42,000
d. 1995 pay increases.......	---	4,497,000	---	+59,000
e. Unemployment compensation	---	4,497,000	---	+4,000
f. Payment for centrally furnished services.....	---	1,608,000	---	+193,000
g. Increased cost of service and supply fund	---	235,000	---	+10,000
h. Increased cost of materials and other supplies...............	---	741,000	---	+24,000
i. Working Capital Fund.....	---	162,000	---	+1,000
j. FTS rate increases.......	---	4,497,000	---	+1,000
Subtotal.................				+378,000

Summary of Changes--Continued

	1994 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Changes:				
B. **Program:**	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.............	375	$ 81,051,000	-28	+$318,000
b. Competing................	129	28,179,000	+13	+3,807,000
2. Research centers............	16	17,343,000	--	+557,000
3. Other research				
a. Research career awards...	43	3,596,000	--	+101,000
b. Cooperative clinical.....	1	1,283,000	--	+36,000
c. Minority biomedical research supplement....	--	530,000	--	+45,000
d. Other research...........	57	2,035,000	--	+90,000
4. Research training				
a. Individual awards........	36	942,000	--	+87,000
b. Institutional awards.....	149	4,202,000	--	+117,000
5. Research and development contracts..................	17	5,741,000	--	+223,000
Subtotal, extramural.....				+5,381,000
6. Intramural research..........	43	9,304,000	--	-127,000
7. Research management and support...................	74	7,110,000	--	-101,000
Net Change............				+5,813,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	117	117	---
Full-time equivalent of overtime and holiday hours	.1	.1	---
Average SES salary	$117,500	$117,500	---
Average GM/GS grade	10.6	10.6	---
Average GM/GS salary	42,318	42,995	+677
Average salary of ungraded positions	20,923	21,258	+335
Personnel Compensation:			
Full-time permanent	$4,534,000	$4,654,000	+$120,000
Other than full-time permanent	1,441,000	1,451,000	+10,000
Other personnel compensation	129,000	149,000	+20,000
Special personnel services	713,000	715,000	+2,000
Total personnel compensation	6,817,000	6,969,000	+152,000
Personnel benefits	1,288,000	1,384,000	+96,000
Benefits to former personnel	5,000	5,000	---
Travel and transportation of persons	334,000	334,000	---
Transportation of things	39,000	39,000	---

	1994 Appropriation	1995 Estimate	Increase or Decrease
Rental Payments to others...........	$426,000	$490,000	+$64,000
Communications, utilities and miscellaneous charges.............	265,000	305,000	+40,000
Printing and reproduction...........	98,000	105,000	+7,000
Other services:			
Consultant services............	250,000	250,000	---
Other services.................	1,630,000	1,699,000	+69,000
Purchases from Govt. accounts..	3,165,000	3,358,000	+193,000
Operation of GOCOs.............	---	---	---
Research and Development Contracts...................	5,741,000	5,964,000	+223,000
Supplies and materials..............	664,000	682,000	+18,000
Equipment...........................	1,433,000	1,226,000	-207,000
Grants, subsidies & contributions...	139,161,000	144,319,000	+5,158,000
Total, budget authority........	161,316,000	167,129,000	+5,813,000

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIDCD

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	4,534	4,534	4,654	120
11.3	Other than full-time permanent	1,441	1,441	1,451	10
11.5	Other personnel compensation	129	129	149	20
11.8	Special personnel services payments	713	713	715	2
11.9	Subtotal, personnel compensation	6,817	6,817	6,969	152
12.1	Civilian personnel benefits	1,288	1,288	1,384	96
13.0	Benefits for former personnel	5	5	5	0
	Subtotal Pay Costs	8,110	8,110	8,358	248
21.0	Travel and transportation of persons	315	334	334	0
22.0	Transportation of things	65	39	39	0
23.2	Rental payments to others	540	426	490	64
23.3	Communications, utilities, and miscellaneous charges	131	265	305	40
24.0	Printing and reproduction	75	98	105	7
25.0	Other Services	1,961	4,295	4,557	262
26.0	Supplies and materials	973	664	682	18
	Subtotal non-pay costs	4,060	6,121	6,512	391
	Total Administrative Costs	12,170	14,231	14,870	639

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1994 House Report	
Tinnitus	
1. The House in its report 103-156, page 66, stated, "The Committee continues to be concerned about tinnitus, a disease that affects many Americans. Within the increase provided for the Institute, the Committee strongly encourages the Institute to allocate additional funding for research on tinnitus."	1. The NIDCD will hold a Workshop on Tinnitus in FY 1995. The workshop will bring together distinguished scientists in many areas of auditory science to analyze the current state of research in tinnitus and to suggest important aspects of the research problem that can be addressed immediately, as well as to develop a long range plan.

Item	Action Taken or to be Taken
1994 Senate Report	
Prevention of hearing loss and deafness	
1. The Senate in its report 103-143, page 108, stated, "The Committee is pleased to learn that scientists are now successfully defining the genetic, dietetic, and environmental factors that interact with aging to produce hearing loss. Studies to understand the mechanisms of age-related hearing loss, measurement of factors that may contribute to such hearing loss, and methods for manipulating these factors should be pursued. The Committee encourages the design and development of clinical trials in this area."	1. NIDCD is pursuing research regarding gene therapy using viral vectors to produce localized transfer of genes to specific cells of the inner ear. Investigator-initiated grant applications for review will be considered for funding on an on-going basis.
Training	
2. The Senate in its report 103-143, page 108, stated, "Training current and future investigators in the communication sciences is an important area in which the NIDCD has devoted much effort. Opportunities for training in the communications sciences should be expanded to allow for the recruitment of young scientists in this critical area. Special emphasis should be placed on pre-doctoral training."	2. The NIDCD is co-sponsoring an innovative training course, the Faculty-Student Partnership Traineeship in Biotechnology in FY 1994. Courses emphasizing recombinant DNA technology will be supported. In addition, a workshop on research training to evaluate mechanisms that would enhance the Institute's existing research training activities is planned for May of 1994.

Tinnitus

3. The Senate in its report 103-143, page 109, stated, "The Committee continues to be concerned about tinnitus, a disease that affects many Americans. Research in this area should continue to be strengthened in order to understand the mechanisms responsible for this condition."

3. The NIDCD will hold a Workshop on tinnitus in FY 1995. The workshop will bring together distinguished scientists in many areas of auditory science to analyze the current state of research in tinnitus and to suggest important aspects of the research that can be addressed immediately, as well as to develop a long range plan.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Funded Authorizations:						
Research and Investigation..........	Section 301	42§241	Indefinite	$156,172,000	Indefinite	$161,781,000
National Institute on Deafness and Other Communication Disorders	Section 464 A-F	42§281	Indefinite		Indefinite	
National Research Service Awards.........	Section 487(d)	42§288	$400,000,000	5,144,000	Such sums as necessary	5,348,000
Total Budget Authority				161,316,000		167,129,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation [1]
1989 [2]	---	---	$87,600,000	$86,530,000
1990	$99,902,000	$99,952,000	121,116,000	118,839,000 [3]
1990 Sequester				-1,256,000
1991	122,847,000	125,623,000 [4]	148,247,000	134,935,000 [5]
1991 Sequester				-2,000
1992	146,321,000	144,495,000	151,106,000	149,102,000 [6]
1993	157,301,000	153,466,000	157,301,000	154,814,000 [7]
1994	153,088,000	162,823,000	162,823,000	162,823,000
1995	167,129,000 [8]			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ The House allowance excluded funds for the unauthorized training programs (National Research Service Awards). The Senate allowance includes the budget for NRSA's. It included up to $93,100,000 for establishment of the proposed new National Institute on Deafness and Other Communication Disorders (NIDCD). The appropriation included the budget of the NRSA program and provided up to $96,100,000 for the establishment of the proposed new institute, NIDCD.

3/ Excludes enacted administrative reductions of $161,000.

4/ Excludes $3,123,000 in NRSA training programs requested but not considered.

5/ Excludes the enacted administrative reduction of $3,562,000.

6/ Excludes the enacted administrative reduction of $1,041,000.

7/ Excludes the enacted administrative reduction of $1,528,000.

8/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communications Disorders

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research												
Deafness and Other Communication Disorders...	---	$121,280	---	$132,748	---	$137,599	---	$144,902	---	$150,283	---	+$5,381
Intramural research.........	31	6,850	38	8,168	44	9,223	43	9,304	43	9,459	---	+155
Research management and support..............	70	6,332	87	7,349	89	7,215	74	7,110	74	7,387	---	+277
Total obligations.........	101	134,462	125	148,265	133	154,037	117	161,316	117	167,129	---	+5,813
Unobligated balance lapsing..................	---	14	---	41	---	121	---	---	---	---	---	---
Total, budget authority.....	101	134,476	125	148,306	133	154,158	117	161,316	117	167,129	---	+5,813

NOTE: Includes FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Institute on Deafness and Other Communication Disorders

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
133	$154,158,000	117	$161,316,000	117	$167,129,000	--	+$5,813,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activites of the National Institute on Deafness and Other Communication Disorders. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Deafness and Other Communication Disorders (NIDCD) is responsible for conducting and supporting research in human communication.

Included in the program areas are research and research training on normal and disordered mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The NIDCD is actively involved in health promotion and disease prevention.

The NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The President's appropriation request of $167,129,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the NIDCD during the last five years has been as follows:

	Amount	FTEs
FY 1990	$117,342,000	61
FY 1991	134,476,000	101
FY 1992	148,306,000	125
FY 1993	154,158,000	133
FY 1994	161,316,000	117

Purpose and Method of Operation

Extramural research and training are supported through seven program areas: hearing, balance, smell, taste, voice, speech, and language. Funding mechanisms include research project grants, research centers, other research grants, research training, and research and development contracts. Intramural research is conducted at three research laboratories and three clinical research branches. The leadership and scientific direction of the Institute are funded through the activity entitled Research Management and Support.

Overall Budget Policy

The FY 1995 budget request for the NIDCD is $167,129,000, an increase of $5,813,000 over the comparable FY 1994 level of $161,316,000.

The FY 1995 budget request for research project grants is $113,355,000, an increase of $4,125,000 or 4 percent over the FY 1994 estimate. The total number of research project grants to be awarded in FY 1995 is 489, compared to 504 in FY 1994. The request level will support 142 new and competing renewal research project grants at an average cost of $225,254. The request will support 347 noncompeting research project grants at an average cost of $233,726.

The NIDCD will support 16 research centers in FY 1995 at $17,900,000, an increase of $557,000 over FY 1994.

Other research grants will total 101 for $7,716,000, a 4 percent increase in funding over FY 1994.

An estimated 185 full-time training positions (FTTP) for $5,348,000 will be supported under the National Research Service Award program, which is the same number as FY 1994 and an increase in funding of $204,000.

The research and development contract budget of $5,964,000 will support 17 contracts, an increase of $223,000 over FY 1994.

The FY 1995 budget request for intramural research is $9,459,000, an increase of $155,000 over FY 1994.

The request for research management and support is $7,387,000, an increase of $277,000 over FY 1994. The request includes 117 FTEs the same number as FY 1994.

National Institute on Deafness and Other Communication Disorders

Extramural Research

Authorizing Legislation - Section 301, 464 A-F, and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$137,720,000	$144,902,000	$150,283,000	+$5,381,000

The NIDCD has primary responsibility at the National Institutes of Health for extramural research and research training in hearing, balance, smell, taste, voice, speech, and language.

Funding for the NIDCD extramural research program during the last five years has been as follows:

	Amount
FY 1990	$107,122,000
FY 1991	121,280,000
FY 1992	132,748,000
FY 1993	137,720,000
FY 1994	144,902,000

Rationale for the Budget Request

With the FY 1995 extramural request these funds will provide support for the following activity: Deafness and Other Communication Disorders program, $150,283,000, an increase of $5,381,000 over the FY 1994 estimate of $144,902,000.

Maternally Transmitted Susceptibility to Aminoglycoside Ototoxicity

Many types of bacterial infections, including tuberculosis, are treated by using aminoglycoside antibiotics. In 3-18% of patients who receive aminoglycoside antibiotics, a drug-induced ototoxicity occurs producing a deficit in hearing or balance. Given the recent public health threat posed by multidrug resistant tuberculosis infections, investigations of ototoxic mechanisms due to aminoglycoside therapy are timely. Hearing loss or balance disorders may also occur in the unborn children of pregnant women who are treated for tuberculosis with these antibiotics. Previous work showed that it is not the antibiotic itself which is ototoxic but rather one of the breakdown products of the chemical reactions in the body called a metabolite, which makes drugs more easily excreted by the body. Recently, investigators have demonstrated that the in vitro formation of the ototoxic metabolite can be prevented by glutathione, a compound important in detoxification. This detoxification compound is normally produced by the body. However, because of the stress of disease such as tuberculosis the body's glutathione response capacity may be compromised. Recent preliminary evidence suggests that glutathione therapy reduces the ototoxicity of aminoglycoside antibiotics without affecting the drugs' antibacterial potency.

Regeneration of Sensory Cells

Disorders of the inner ear had long been considered irreversible, but research over the past several years has shown that, under certain conditions, sensory cell production in the auditory system can be reactivated and that regenerated cells establish functional neural connections. Most recently, hair cell regeneration in the vestibular sense organs of adult mammals has been documented. Shortly after drug-induced loss of hair cells, supporting cells of both guinea pig and human inner ear vestibular tissue begin dividing in culture and subsequently exhibit the characteristics of immature hair cells. This dramatic finding raises the possibility that in mammals, including humans, the vestibular sense organ may be stimulated to recover its function. With this definitive knowledge, research will continue into looking for cures for sensorineural hearing loss.

Cochlear Implants

The cochlear implant is a surgically placed electronic device which restores partial hearing to individuals with profound hearing impairment. The implant does not amplify sounds, but rather, bypasses damaged portions of the inner ear and electronically stimulates the hearing nerve. Efforts to increase knowledge about the optimal use of cochlear implants and their related speech processors in adults and children are continuing. New findings indicate that electrical stimulation in mammals can reverse deafness-related central auditory nervous system changes in some instances. When the deafness is long-term, however, central auditory system changes are not as readily reversed and stimulation with a cochlear implant may not be sufficient to induce change. Improved performance with cochlear implants occurs over a more extended period of time.

Investigators are also continuing to understand more about the ability of deaf children to use cochlear implants to acquire speech skills. Longitudinal studies of speech perception in children using cochlear implants compared children who were congenitally deaf with children who had an onset of deafness after birth but before age 3. No significant differences were found between the scores for the two groups on most of the speech perception tests administered.

Hereditary Hearing Impairment

Molecular genetics of hereditary hearing impairment is one of the highest research priorities of the NIDCD. Recent evidence suggests that the development of some hearing deficits may be dependent on the presence of several genes. While the disposition to develop deafness may be carried in one gene, the actual manifestation of deafness may be dependent on the concomitant presence of other genes. Recent work on two different forms of hereditary hearing impairment, Usher syndrome and Waardenburg syndrome, suggests that multiple genes must be present to produce these forms of deafness. Research on the development of the deafness associated with Waardenburg syndrome shows a dependence on genetic information contributed by both parents. The data explain why certain members of families who carry the Usher or Waardenburg gene may have normal hearing. Research is needed to continue to identify the genes and the combination of genes that cause hereditary hearing impairment for better diagnosis, genetic counseling and possible future gene therapy.

Role of Melanocytes in Protection Against Noise Damage

Contrary to previous assumptions, new evidence indicates that pigment cells, called melanocytes, in the adult inner ear undergo continuing replication. Similarity between the melanocytes found in the inner ear and those found in the skin are being identified. The ability of pigment cells to stabilize and promote tissue repair in the skin has been assumed to underlie postinflammatory changes in skin pigmentation that occur after such events as burns, mechanical injury or ultraviolet radiation exposure. A continuation of this exciting research will determine if the inner ear may be stabilized and protected by mechanisms involving the melanocytes from damaging conditions such as repeated noise exposure.

Transplant Potential of the Olfactory Epithelium

When pieces of the olfactory neuroepithelium are transplanted into the brain, the olfactory tissue thrives and its stem cells divide, giving rise to new receptor neurons that develop, mature and connect with target tissue in the brain. Since olfactory nerves have the ability to pass barriers that impede other nerve cells, olfactory transplants have the potential to serve as pathways for the reconnection of injured neurons with their targets. Transplants of olfactory neuroepithelium provide a potential new approach for the biological repair of nerve damage resulting from age, injury and neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Treatment of Otitis Media

Children under six years of age are taken to the doctor for the treatment of otitis media more frequently than for any other childhood illness. Ninety per cent of children in this age group are treated at least once for otitis media. In addition to the cost of examinations and treatment, there is substantial, and often repeated, cost in lost work for the parents. Recent studies in children show that even when hearing returns to normal following an episode of otitis media, some aspects of auditory processing remain abnormal. Consequently, hearing tests that measure only auditory sensitivity may not accurately assess damage to the auditory system produced by otitis media. Scientists have also found the immunological response of the body to middle ear infection actually inhibits the ability of certain antibiotics to be transported into the middle ear complicating treatment. It is also possible that beginning antibiotic therapy too early may actually produce a "blunted" immune response and an enhanced susceptibility to reinfection. Additional research will further explore how the choice of drug and the timing of drug therapy may be crucial determinants of therapeutic effectiveness and potential for disease recurrence.

Presbycusis

Presbycusis is the hearing loss that often accompanies aging. NIDCD scientists are focusing on the relationship between structural and molecular changes associated with aging in the capillary system of the inner ear. This research will provide a better understanding of the processes underlying presbycusis. Immunohistochemical evaluations show that transports systems of electrically charged atoms or ions in the inner ear of gerbils degenerate as a function of age. These findings, in conjunction with previous work on human temporal bones, suggest that a considerable amount of the hearing loss of presbycusis may be associated with a decreased electrical capability of the cochlea or endocochlear potential. The research further suggests possible methods for intervention and treatment designed to reestablish a normal endocochlear potential. For example, current injection or infusion of selected ions into the inner ear may prevent further deterioration in hearing in appropriate individuals.

Physiological and Molecular Bases of Tinnitus

An estimated 15% of Americans suffer from ringing, roaring or buzzing sounds in the ear or head, known as tinnitus. Tinnitus usually occurs in association with disorders of hearing and balance. The symptom of tinnitus can be produced by a variety of pathological conditions, but progress in the study of tinnitus has been limited by too few animal models. Pharmacological agents (salicylates or quinine), known to produce tinnitus in humans, have resulted in the apparent perception of sound in animals. Current findings suggest that altered calcium release in the inner ear appears to play a role in the "tinnitus-like" symptoms in these animals. Decreases of free calcium in the perilymph, a fluid contained in the inner ear, correlates with the induction of salicylate- or quinine-induced tinnitus at certain dosage levels. Preventing changes through dietary calcium supplementation or calcium channel blockers reversed the tinnitus indicative behavior in the animals studied. Research progress which helps to ameliorate or eliminate the symptom of tinnitus will have a significant public health impact, both socially and financially.

Advances in Smell, Taste and Bionutrition

Studies of the relationship between nutrient intake and smell and taste function are important in the development of strategies to modify the dietary intake of individuals with various medical conditions. Investigators recently found that providing premature tube-fed infants with a sweet-flavored nipple promotes earlier progression to oral feeding. Such strategies are needed to ensure a premature infant's opportunity to thrive. Other studies have found that patients with distortions of smell or taste tend to lose weight. This research could have significant implications for nutrition of the aging and the very young. Additionally, scientists have redesigned monellin, an intensely sweet protein that is low in calories and does not induce tooth decay, with the aid of molecular genetic and crystallographic techniques. By identifying the molecular site of monellin that is recognized by the sweet taste receptor, the design of even more effective sweet proteins may be possible. Such knowledge is important in formulating effective dietary intervention strategies. The NIDCD recently lead a trans-NIH initiative on chemosensory/bionutrition research and will continue to collaborate with other NIH components engaged in bionutrition research.

Human Vomeronasal Organ

Pheromones are the biological signals that influence sexual and reproductive behaviors. Pheromones are detected by the vomeronasal organ in lower animals. Although the vomeronasal organ is present in the human fetus, it was thought to disappear in humans by the time of birth. Recent studies of biopsied human tissue reveal a specialized epithelial organ in the appropriate location whose cells express features resembling the neurons found in the main olfactory neuroepithelium. In animals, the vomeronasal organ sends messages to the hypothalamus, a part of the brain involved with emotions and drives. While current studies provide evidence that a vomeronasal organ may indeed be present in adult humans, further studies are needed to determine whether this structure influences human behavior.

Advances in Assistive Devices for Hearing-Impaired Persons

Scientists participating in the NIDCD Small Business Innovation Research program have improved vibrotactile devices that amplify and modify sound energy so that its vibrations can be perceived through the skin. For individuals where hearing impairment presents a threat to safety, work is underway to develop a novel signal processing system that will alert them to important household, workplace, and environmental sounds. An assistive listening device that incorporates many modern technologies (including infrared and frequency modulation (FM) into a single device was brought to the market in 1993. The microphone designed for use in this device has proven to be of great benefit in noisy situations and shows promise for application in other assistive listening devices including hearing aids and cochlear implants.

Central Auditory System Plasticity and Reorganization

In studies of adult animals including primates, NIDCD investigators have discovered that parts of the audiotory cortex undergo reorganization as a result of cochlear damage. This damage can be the result of destruction caused by some medications. Adjoining regions of the brain, which process information from undamaged cochlear regions, essentially "take over" the space previously dedicated to processing information from the now damaged cochlear regions. Additionally, portions of the brain can, in a short period of time, change their response to environmental stimuli that are important to an individual's health and well-being. These previously unsuspected changes appear to be quite common in adults and may help provide insights into normal adult learning and memory. Understanding such changes may permit the development of treatments for learning and memory disorders.

Treatment of Phonological Disorders in Children

Phonemes are the specific, meaningful units that make up languages and allow analysis of the aquisition of spoken language. Many children require clinical intervention to bring their phonology, the meaningful speech sounds of a specific language, into conformity with the language they are learning. Clinical intervention for children with phonological disorders has been based on the premise that speech sound development proceeds through a fixed series of stages with one sound prerequisite for the emergence and mastery of other sounds--a developmental approach. New research findings suggest that the greatest gains in sound perception and sound production learning for children with phonological disorders may be achieved by abandoning the developmental approach and refocusing clinical treatment on later-acquired sounds. Investigators have found that, contrary to conventional clinical practice, treatment for later-acquired sounds results in more extensive phonological change than treatment for earlier-acquired sounds.

The Induction of Smell Sensitivity

Many individuals suffer from an inability to detect specific odors. This is a problem that becomes more common and more dangerous in the elderly. While some of these odor identification deficits are known to have a genetic basis, scientists have recently found that in some instances, environmental factors, such as exposure to particular smells, can modulate genetic deficits. Almost 50% of adults cannot smell the volatile steroid androstenone. Half of the participants in a recent study who were initially unable to smell androstenone were induced to detect the odor by repeated exposure to it over a six-week period. This is the first demonstrated correction of a genetic defect in smell by a chemosensory experience. Further investigations will assess whether such induction is possible with other substances and attempt to uncover the molecular mechanisms that regulate the induction of odor perception.

Autoimmunity in Ménière Disease

The most consistent inner ear abnormality associated with Ménière disease is the ballooning of the membrane walls of the inner ear resulting from excessive fluid. The actual cause of the disease is, however, unclear. Over the last ten years, evidence has accumulated that suggests Ménière disease may represent an immune reaction mounted by the body against portions of the inner ear tissue. Investigators are searching for the antibodies that are induced by and react with inner ear antibodies in patients diagnosed with Ménière disease. If specific inner ear antibodies can be related to Ménière disease, a much-needed clinical diagnostic test for this debilitating disorder can be developed and specific treatment can be developed.

Language and Cognition

Williams syndrome (WMS) is a genetic disorder characterized by peculiar facial features, cardiac and dental anomalies, hypercalcemia, and mental retardation. Recent studies of children with WMS challenge the belief that the level of language ability of retarded children tends to be equal to or below their level of functioning in other cognitive areas. Despite the presence of severe general cognitive deficits, linguistic abilities are selectively preserved in WMS. This "sparing" of linguistic abilities has been documented in adolescent WMS individuals. Recent studies of younger children with WMS indicate extreme retardation early on in all developmental milestones, including language. Although young WMS children and children with

Down syndrome are remarkably similar in their language delays, they exhibit dramatically different skills once they reach adolescence. By uncovering differences between the two groups in the early stages of prespeech and language development, insights will be gained in what causes the contrasting abilities in language and cognition that are evident in adolescence.

NIDCD-DVA Hearing Aid Initiative

The NIDCD and the Department of Veterans Affairs (DVA) are progressing in their joint plan for hearing aid research and development. The first program announcement under this cooperative venture was published in 1993 and focuses on speech understanding with hearing aids in quiet and noisy environments. Activities planned for 1994 include: the publication of a second program announcement to determine ways to evaluate the benefit received from hearing aids; a contract award to design and evaluate new strategies and technologies for hearing aids; and, the writing of a clinical trial protocol. Clinical trials are scheduled to begin in 1995 through an interagency agreement with the DVA, and a national forum that same year will facilitate the exchange of information in hearing aid research and development.

NIDCD-NASA Center for Vestibular Research

In August 1993, the NIDCD and the National Aeronautics and Space Administration jointly funded a multi-institutional center for integrated research and research training on the vestibular control of balance during standing posture, locomotion and other purposeful movements. The scientific goals of the Center, comprising eighteen investigators at six institutions, include developing a whole-body model of human posture, delineating the contributions of each biomechanical component of the model, and predicting the role of inputs from the vestibular system to the reflexes that facilitate head and body stability during standing posture and movement.

ASL Dictionary

Because American Sign Language (ASL) is not written and demands spatial presentation and movement, it has never been available in an easily and instantly accessed, appropriate visual dictionary format. Investigators supported by a Phase 2 SBIR are creating an ASL-English Dictionary on CD-ROM which will display the ASL equivalent of a typed English word in full motion video on the computer screen. Other reference capabilities will include sign use within a phrase, synonyms, antonyms, and historical and linguistic information. Investigators anticipate the use of this system in libraries and sign language programs across the United States and Canada.

National Institute on Deafness and Other Communication Disorders

Intramural Research Program

Authorizing Legislation - Section 301, 464 A-F, and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
44	$9,223,000	43	$9,304,000	43	$9,459,000	--	+$155,000

The mission of the NIDCD Intramural Research Program is to conduct basic and clinical research on the normal processes and diseases and disorders of hearing, balance, smell, taste, voice, speech and language.

These efforts range from basic multidisciplinary biological research to clinical trials of newly developed medical and surgical therapies. The Laboratories and Research Clinics are located at the NIH in Bethesda, Maryland.

Funding for the Intramural Research Program during the last five years has been as follows.

	Amount	FTEs
FY 1990	$5,159,000	22
FY 1991	6,850,000	31
FY 1992	8,168,000	38
FY 1993	9,223,000	44
FY 1994	9,304,000	43

Rationale for the Budget Request

The FY 1995 budget request for intramural research is $9,459,000, an increase of $155,000 over the FY 1994 level of $9,304,000. The following highlights a few research activities in the NIDCD intramural research program:

Nonsyndromic Sensorineural Hearing Impairment

Investigators in the NIDCD intramural program recently located a sex-linked gene on the short arm of the X-chromosome that, when mutated, causes nonsyndromic sensorineural hearing impairment. This mutated gene represents a new locus on the X-chromosome for nonsyndromic hearing impairment and is distinct from other forms of X-linked hearing impairment that have been previously identified. The mutation is especially interesting because it is located within the gene responsible for Duchenne muscular dystrophy (DMD), a disorder that has not been associated with hearing impairment. To explore the relationship between the nonsyndromic hereditary hearing impairment identified in this family and DMD, additional studies will examine whether dystrophin, the protein product of the DMD gene, is present in the inner ear. Evidence of hearing impairment in patients diagnosed with DMD will be sought.

Imaging Techniques

Modern imaging techniques are being used by several investigators to improve the diagnosis and treatment of communication disorders. Scientists in the Institute's intramural voice and speech program are comparing information on cortical structure provided by magnetic resonance imaging with information on cortical function provided by positron emission tomography in patients with a variety of speech disorders. For example, using positron emission tomography to study cerebral blood flow, intramural scientists have recently completed the first study of differences in brain activity between individuals with normal and stuttered speech. In normal speakers, brain activity was symmetric between the two sides, with a slight predominance in the left hemisphere, during oral movements and nonsense speech. As soon as meaningful speech was used, brain activity became dominant in the left hemisphere. In a similar study of speakers who stutter, a slight predominance of activity in the right hemisphere during oral movements and nonsense speech was demonstrated. When the stuttering subjects used meaningful speech, increases in activity in the left hemisphere were not shown. Singing, however, was associated with right hemisphere activation in the normal speakers while the stuttering subjects showed bilateral activation. These are the first findings of an absence or reversal of functional brain asymmetries in stuttering subjects and suggest new directions for determining the brain bases for stuttering. Studies such as these will allow investigators to correlate structure with function and thereby improve understanding of the neurogenic basis of speech disorders.

Other scientists are using computerized tomography (CT) to predict the success of several treatments for aphasia. The results of one study indicated that information from both the CT and a language assessment performed by a speech-language pathologist may accurately predict whether one method of treatment, melodic intonation therapy, will improve the ability to communicate.

Development of Vaccines Against Otitis Media

Otitis media is the most common childhood infection requiring antibiotic therapy. It is the major cause of acquired hearing impairment in childhood. NIDCD intramural scientists are collaborating with scientists from the National Institute of Child Health and Human Development, NIH, and the Center for Biologics Evaluation and Research, FDA, to attempt to identify suitable vaccine (antigen) candidates for developing conjugate vaccines.

Multiple-Drug Resistant Tuberculosis

Several aspects of communication disorders that have bearing on multiple-drug resistant tuberculosis (MDR-TB) are under investigation. The Voice and Speech Section is currently studying the neurophysiologic characteristics of vocal cord paralysis and biomechanical modeling of laryngeal muscles. Other scientists are investigating tuberculosis of the larynx, laryngeal tissue augmentation following treatment of tuberculosis of the larynx, and application of biomechanical modeling to reconstructive and neuroprosthetic rehabilitation of the larynx following control of tuberculosis. Also under study are the molecular mechanisms of aminoglycoside ototoxicity and measurement of otoacoustic emissions as a means of early detection of aminoglycoside ototoxicity.

cDNA Libraries

The NIDCD shares the world's optimism for the opportunities provided by molecular biology and specifically the application of molecular genetics and is conducting and supporting research that explores the molecular mechanisms associated with communication disorders. In that effort, NIDCD intramural scientists have constructed several cDNA libraries. One cDNA library represents genes found in the organ of Corti (the hearing organ in the inner ear), and another cDNA library has been constructed from messages expressed in the crista ampullaris (a vestibular organ in the inner ear). Genes common to both cDNA libraries, but not found in other places in the body, are most likely to be involved with sensory transduction and homeostasis of hair cells. Identifying these genes will enhance our understanding of communication disorders on a molecular level.

National Institute on Deafness and Other Communication Disorders

Research Management and Support

Authorizing Legislation - Section 301, 464 A-F, and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
89	$7,215,000	74	$7,110,000	74	$7,387,000	--	+$277,000

This activity provides the staff and resources for the scientific leadership and overall management and direction of the Institute. It is composed of the staff of the Office of the Director and the Extramural Program. It involves a wide range of functions, including administration, selection of promising research areas for new or expanded investigation, and implementation of new initiatives. Also supported are Institute data systems, public information activities, and management of the Institute's diverse grant portfolio.

Funding for the Research Management and Support during the last five years has been as follows:

	Amount	FTEs
FY 1990	$5,061,000	31
FY 1991	6,346,000	70
FY 1992	7,390,000	87
FY 1993	7,215,000	89
FY 1994	7,110,000	74

Rationale for the Budget Request

The FY 1995 budget request for research management and support is $7,387,000, an increase of $277,000 over the FY 1994 level of $7,110,000.

NATIONAL INSTITUTES OF HEALTH

National Institute on Deafness and Other Communication Disorders

Detail of Full-time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director...........	14	14	14
Office of Administration..........	38	33	33
Division of Intramural Research...	44	43	43
Division of Extramural Activities.	20	15	15
Division of Communication Sciences and Disorders..........	17	12	12
Total, NIDCD.................	133	117	117

Average GS/GM Grade

1990...........................	9.5
1991...........................	9.6
1992...........................	9.6
1993...........................	10.0
1994...........................	10.6
1995...........................	10.6

NOTE: Includes FTEs associated with HIV research activities. Funds to support theses FTEs are included in the NIH Office of AIDS Research.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FISCAL YEAR 1995

Volume VI

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health
National Institute on Drug Abuse
National Institute on Alcohol Abuse and Alcoholism
National Center for Research Resources
National Institute of Nursing Research

Justification of
Estimates for
Appropriations Committees

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

	FY 1995 Estimate		Page
	FTEs	Amount	Number
National Institute of Mental Health...	929	$545,223,000	1
National Institute on Drug Abuse......	390	291,963,000	43
National Institute on Alcohol Abuse and Alcoholism.....................	237	182,498,000	81
National Center for Research Resources..........................	100	286,394,000	113
National Institute of Nursing Research...........................	51	48,326,000	145

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

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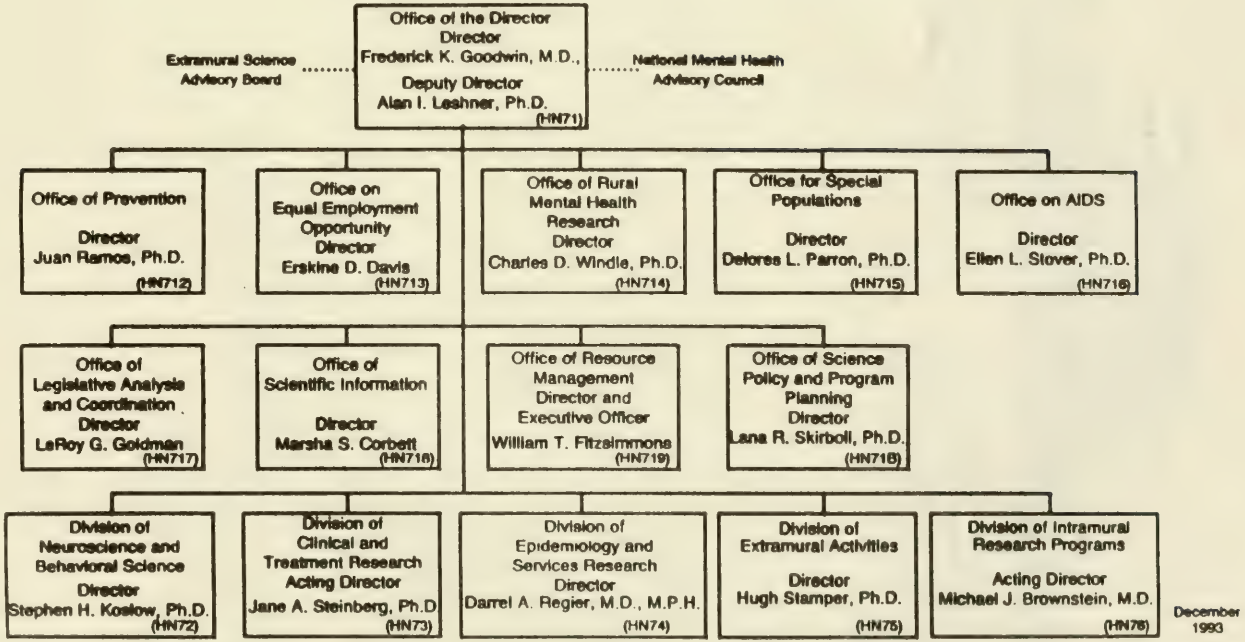
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institute of Mental Health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Deputy Director
Alan I. Leshner, Ph.D.
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National Mental Health Advisory Council
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Division of Intramural Research Programs
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Michael J. Brownstein, M.D.
(HN76)
December 1993

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

For carrying out section 301 and title IV of the Public Health Service Act with respect to mental health, [$613,444,000] *$545,223,000, of which $6,679,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriation Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Language Analysis

Language Provision	Explanation
"...of which, $6,679,000 shall not become available for obligation until September 19, 1995."	This language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$590,436,000	$613,444,000	$545,223,000
Section 511 .8% Reduction	-4,723,000	---	---
Section 513 Consultant services reduction	-81,000	---	---
Section 216 S & E Reduction	-1,981,000	---	---
Subtotal, adjusted appropriation	583,651,000	613,444,000	545,223,000
Real transfer to other NIH accounts for tuberculosis research	-509,000	---	---
Comparative transfer to the Office of AIDS Research, NIH for HIV activities	-78,433,000	-87,182,000	---
Subtotal, adjusted budget authority	504,709,000	526,262,000	545,223,000
Unobligated balance, lapsing	-291,000	---	---
Total obligations	504,418,000	526,262,000	545,223,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1993--$5,587,000; 1994--$7,300,000 and 1995--$7,210,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Mechanism

Research grants:	1993 Actual No.	1993 Actual Amount	1994 Appropriation No.	1994 Appropriation Amount	1995 Estimate No.	1995 Estimate Amount
Research projects:						
Noncompeting	844	$193,666,000	825	$188,064,000	888	$201,612,000
Administrative supplemental	(22)	1,076,000	(22)	1,121,000	(22)	1,167,000
Competing projects:						
Renewal	125	31,644,000	173	45,517,000	167	46,012,000
New	166	24,164,000	229	34,757,000	221	35,136,000
Supplemental	2	114,000	3	164,000	3	166,000
Subtotal, competing	293	55,922,000	405	80,438,000	391	81,314,000
Subtotal, research projects	1,137	250,664,000	1,230	269,623,000	1,279	284,093,000
Research centers:						
Spec./comp. centers	52	49,478,000	54	52,830,000	54	55,001,000
Other Research:						
Research career programs	246	25,100,000	251	26,179,000	251	26,912,000
Cooperative clinical research	5	1,198,000	5	1,403,000	5	1,442,000
Other research related	151	23,671,000	176	23,427,000	174	23,814,000
Subtotal, other research	402	49,969,000	432	51,009,000	430	52,168,000
Total, research grants	1,591	350,111,000	1,716	373,462,000	1,763	391,262,000

Training:						
Individual awards:						
Noncompeting....................	107	1,977,000	109	2,062,000	109	2,120,000
Competeting......................	123	2,467,000	126	2,573,000	126	2,645,000
Subtotal, individual..........	230	4,444,000	235	4,635,000	235	4,765,000
Institutional awards:						
Noncompeting....................	782	17,482,000	756	18,233,000	756	18,744,000
Competing.......................	134	3,225,000	129	3,364,000	129	3,458,000
Subtotal, institutional.......	916	20,707,000	885	21,597,000	885	22,202,000
Total, training....................	1,146	25,151,000	1,120	26,232,000	1,120	26,967,000
Research & development contracts......	42	10,447,000	42	10,922,000	42	11,228,000
	FTEs		FTEs		FTEs	
Intramural research program...........	590	87,020,000	634	84,862,000	614	84,936,000
Research management and support.......	358	31,980,000	323	30,784,000	315	30,830,000
Extramural construction..............	---	---	---	---	---	---
Total, NIMH.........................	948	504,709,000	957	526,262,000	929	545,223,000
(Clinical Trials)...............		(41,088,000)		(43,034,000)		(44,630,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Summary of Changes

1994 Estimated budget authority	526,262,000
1995 Estimated budget authority	545,223,000
Net Change	+18,961,000

	1994 Current Estimate Base		Change from Base	
Changes:	FTE	Budget Authority	FTE	Budget Authority
A. Built-in:				
1. Intramural:				
a. Within grade increase		$36,190,000		+$423,000
b. One less day of pay		36,190,000		-139,000
c. Annualization of January 1994 locality pay raise.		36,190,000		+383,000
d. January 1995 pay increases		36,190,000		+434,000
e. FECF, Unemployment compensation		36,190,000		+22,000
f. Service and supply fund increase		8,568,000		+291,000
g. Payment for centrally funded services		28,461,000		+1,170,000
h. Increased FTS costs		321,000		+9,000
i. Increased cost of laboratory materials and supplies		11,322,000		+347,000
Subtotal				+2,940,000
2. Research Management & Support:				
a. Within grade increase		19,799,000		+282,000
b. One less day of pay		19,799,000		-76,000
c. Annualization of January 1994 locality pay raise.		19,799,000		+209,000
d. January 1995 pay increases		19,799,000		+238,000
e. FECF, Unemployment compensation		19,799,000		+12,000
f. Payment for centrally funded services		1,234,000		+51,000
g. DHHS Working Capital Fund.		603,000		+5,000

Summary of Changes--continued

	1994 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
h. Increased FTS costs.......		143,000		+4,000
i. Service and supply fund increase................		3,684,000		+334,000
j. Increased cost of material and other supplies......		5,464,000		+153,000
Subtotal.............				+1,212,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting.............	825	189,185,000	+63	+13,594,000
b. Competing................	405	80,438,000	-14	+876,000
Total, research projects.	1,230	269,623,000	+49	+14,470,000
2. Research centers.............		52,830,000		+2,171,000
3. Other research...............	432	51,009,000	-2	+1,159,000
4. Research training............		26,232,000		+735,000
5. Research and development contracts..................		10,922,000		+306,000
	FTE		FTE	
6. Intramural research program...	634	84,862,000	-20	-2,866,000
7. Research management & support.	323	30,784,000	-8	-1,166,000
Subtotal..................				+14,809,000
Total changes................				+18,961,000

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NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Authority By Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	957	929	-28
Full-time equivalent of overtime and holiday hours.......	5	5	--
Average ES salary..................	$110,970	$112,302	$1,332
Average GM/GS grade................	10.2	10.2	0.0
Average GM/GS salary...............	$43,494	$44,016	$522
Average salary, grades established by PHS Act of 1955 (42 USC 207)..	$51,538	$52,156	$618
Average salary of ungraded positions.......................	$33,715	$34,119	$404
Personnel compensation:			
Full-time permanent................	30,185,000	30,060,000	-$125,000
Other than full-time permanent.....	8,974,000	8,947,000	-27,000
Other personnel compensation.......	1,777,000	1,771,000	-6,000
Special personnel service payments.	4,202,000	4,189,000	-13,000
Total personnel compensation....	45,138,000	44,967,000	-171,000
Personnel benefits....................	9,516,000	9,493,000	-23,000
Benefits for former personnel.........	32,000	32,000	---
Travel and transportation of persons..	947,000	952,000	+5,000
Transportation of things..............	173,000	174,000	+1,000
Rental payments to others.............	1,561,000	1,572,000	+11,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Communications, utilities, and miscellaneous charges...............	$1,431,000	$1,440,000	+$9,000
Printing and reproduction............	827,000	833,000	+6,000
Other services:			
Consulting services.................	1,784,000	1,797,000	+13,000
Other services......................	6,333,000	6,273,000	-60,000
Purchases from government accounts..	36,853,000	37,362,000	+509,000
Research & development contracts....	10,922,000	11,228,000	+306,000
Supplies and materials................	6,350,000	6,373,000	+23,000
Equipment............................	4,701,000	4,498,000	-203,000
Grants, subsidies, & contributions....	399,694,000	418,229,000	+18,535,000
Total, budget authority by object	526,262,000	545,223,000	+18,961,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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National Institutes of Health
Administrative Costs
Budget Authority
NIMH

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	30,185	30,185	30,060	(125)
11.3	Other than full-time permanent	8,974	8,974	8,947	(27)
11.5	Other personnel compensation	1,777	1,777	1,771	(6)
11.8	Special personnel services payments	4,202	4,202	4,189	(13)
11.9	Subtotal, personnel compensation	45,138	45,138	44,967	(171)
12.1	Civilian personnel benefits	9,516	9,516	9,488	(28)
13.0	Benefits for former personnel	32	32	32	0
	Subtotal Pay Costs	54,686	54,686	54,487	(199)
21.0	Travel and transportation of persons	1,294	947	952	5
22.0	Transportation of things	244	173	174	1
23.2	Rental payments to others	21	1,561	1,572	11
23.3	Communications, utilities, and miscellaneous charges	3,074	1,431	1,440	9
24.0	Printing and reproduction	863	827	833	6
25.0	Other Services	54,654	44,970	45,437	467
26.0	Supplies and materials	6,282	6,350	6,373	23
	Subtotal non-pay costs	66,432	56,259	56,781	522
	Total Administrative Costs	121,118	110,945	111,268	323

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1994 House Report	
Eating Disorders	
1. The House in its report 103-156, page 67 stated "The Committee is encouraged by the Institute's emphasis on eating disorders and is pleased with the technical assessment conference on eating disorders held in May, 1993. The Committee encourages the Institute to continue to follow up on the conference by initiating a public and professional eating disorders education campaign as directed in last year's report. The Committee expects the Institute to fully comply with the 1993 House directive by the end of fiscal year 1994."	1. NIMH has continued to examine the field of eating disorder research to assess the feasibility of a public education campaign. Because these prevention and treatment fields are so new, NIMH is aggressively fostering them to ensure an adequate knowledge base for a public education campaign. For example, NIMH has worked with the McKnight Foundation Eating Disorders Program to develop a multi-site, common protocol, that includes a prevention module. Following these pilot studies, NIMH expects to fund large scale research, research training, a data center, and particularly an information center. NIMH is also supporting treatment trials of cognitive/behavioral therapy, medication, and the combination therapy. Comorbidity of eating disorders with other mental disorders is a severe problem that is under consideration for a program announcement. NIMH is cooperating with the American Psychiatric Association in developing treatment guidelines. In addition, to raise awareness of symptoms, NIMH is coordinating with the SAMHSA Center for Mental Health Services which has a mandate to disseminate public information on eating disorders and the Office of Women's Research at the Department of Health and Human Services.

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Item	Action Taken or to be Taken
1994 Senate Report	
Behavioral Science Task Force	
1. The Senate in its report 103-143, page 114 stated, "The Committee understands that the NIMH National Advisory Council is in the midst of a major effort to develop a behavioral science research agenda. It has convened a distinguished behavioral science task force of outside experts and they are now conducting a comprehensive assessment of the basic behavioral and psychosocial research. The result should be a national plan for behavioral science research similar to other NIMH reports that have shaped the Institute's programs in schizophrenia, child and adolescent mental disorders, and neuroscience. The Committee applauds this effort and is looking forward to receiving the task force report when it is presented to the NIMH National Advisory Council. Further, the Committee requests NIMH to report back to Congress within 60 days of the final task force report with plans for implementing the recommendations of the task force."	1. A first draft of the report is in progress. Following approval of the report by the National Advisory Mental Health Council, NIMH will develop an implementation plan and will forward those recommendations to the Congress.
Social Work Research	
2. The Senate in its report 103-143, page 115 stated, "The Committee instructs the NIMH to continue its efforts and activities directed toward developing social work research resources, including social work research development centers and targeting training initiatives for social work researchers, giving particular attention to the need to develop a cadre of	2. NIMH established the first social work research development center in FY 1993 and continues its commitment to develop these centers and research training opportunities. A report to the Congress has been prepared and it is currently in review.

Item	Action Taken or to be Taken
(continued) minority researchers, including native Americans. The Committee expects the recommendations of the task force on social work research to be fully implemented and requests regular reports on the status of the implementation.	
Child and Adolescent Mental Health	
3. The Senate in its report 103-143, page 115 stated, "NIMH has supported prevention research over the past 10 years, and the Committee further notes that while the program is a small one, this research has led to major advances in the development of prevention interventions, particularly with respect to mental disorders among children and adolescents, in the area of suicide attempts among adolescents and adults, and in addressing issues of stress and coping among young adults. The Committee directs NIMH to fully support the six currently funded projects and to fund one additional project in this promising, innovative, and scientifically rigorous area of research. The Committee further urges NIMH and the Center for Mental Health Services to collaborate to ensure continued support for the program, and to ensure that the knowledge gained from this research is communicated effectively to prevention service providers."	3. In FY 1994, NIMH will fully support five prevention demonstrations for child and adolescent mental disorders. This is one less than in FY 1993 because one project will not return for funding. In FY 1994, the Institute has not yet received any additional applications for this type of research funding. The Institute is collaborating with the SAMHSA Center for Mental Health Services to disseminate the results of our prevention research. In addition, we are distributing widely the recent report of the NIMH Prevention Research Steering Committee, "The prevention of Mental Disorders: A National Research Agenda" and the Institute of Medicine Report, "Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research."
Rural and Native American Research	
4. The Senate in its report 103-143, page 115 stated, "The Committee has set aside funds every year since fiscal year 1990 for rural and native	4. For FY 1993, the Committee directed NIMH to spend $15,000,000 for research on rural and native American mental health issues. The Institute

Item	Action Taken or to be Taken
(continued)	(continued)
American mental health research. The Committee commends NIMH for responding to the need for increased research on rural mental health issues, and particularly for developing three rural mental health research centers. These centers have achieved national stature and have contributed significantly to advancing rural mental health research. The Committee is concerned, however, that NIMH did not meet the Committee's fiscal year 1993 directive to allocate appropriate funding for rural mental health research and for research on mental health among native populations. The Committee has provided additional funds for the NIMH to increase its funding of rural and native American mental health research. The Committee intends that funds for rural mental health research be targeted primarily to existing research centers to promote individual and collaborative research that will be truly regional and national in scope. The Committee continues to place high priority on research with a focus on family, community, and individual characteristics that promote or impair mental health in rural areas, and also the study of services to improve mental health in rural communities."	estimates that it spent $17,373,000 on rural research. Of this, approximately $13,700,000 involved psychosocial and services delivery research while the remainder was for psychiatric research. A further $3,438,000 was spent on native American mental health research. NIMH encourages research on rural problems through a special announcement and has funded three rural research centers. Three more centers with primary foci on service provision or youth behavior also concentrate on rural populations. In FY 1994, NIMH intends to increase these levels of support.
Alzheimer's disease	
5. The Senate in its report 103-143, page 116 stated, "The Committee is pleased to note that NIMH has accorded high priority to research on Alzheimer's disease, and expects that funding support will	5. NIMH estimates that approximately $25,300,000 will be used to fund the Institute's FY 1994 Alzheimer's disease research programs, an increase of $1,115,000 over FY 1993. NIMH collaborates with the

Item	Action Taken or to be Taken
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continue to grow. As the National Institute on Aging proceeds with work on a long-range plan for Alzheimer's research, the Committee encourages NIMH to lend its unique perspective and recommendations to the effort."	National Institute on Aging through membership on the Advisory Panel on Alzheimer's Disease, the Advisory Council on Alzheimer's Disease, and the Task Force on Aging Research.
Positron Emission Tomography	
6. The Senate in its report 103-143, page 116 stated, ". . . The Committee encourages the Institute to expand support for research regarding the diagnostic applications of positron emission tomography in children and to utilize the expertise of PET facilities dedicated to the treatment of children's diseases and affiliated with other medical research and teaching institutions."	6. NIMH does not currently support any studies using PET in children for diagnosis or any other research protocol. PET studies in adolescents and adults have produced results that were applicable to childhood disorders such as Attention deficit/hyperactivity and schizophrenia. PET studies include a small but real risk of radiation. Due to difficulties with informed consent and ethical considerations, NIMH recommends caution in the use of PET for diagnosis in this population.
Human Brain Project	
7. The Senate in its report 103-143, page 116 stated, "The Committee was pleased to receive the report from the NIMH on the human brain project which it had requested last year. The Committee would like to be kept apprised of the progress of this effort and directs the NIMH to submit an update on the human brain project prior to next year's hearings."	7. The first Human Brain Project grant awards were made in FY 1993. NIMH and other agencies continue their support for and commitment to the Human Brain Project. A report to the Congress has been prepared and it is currently in review.
Mental Health Service Needs of Children	
8. The Senate in its report 103-143, page 116 stated, ". . . more must be learned about	8. NIMH has been working toward a major, multi-site, child and adolescent study with three main

Item	Action Taken or to be Taken
(continued)	(continued)
children's unique services needs and usage through a research effort aimed at clarifying what is known and unknown about the special service delivery needs of this vulnerable population. NIMH is also urged to magnify its efforts to address the critical shortage of researchers in the area of child and adolescent mental health, which has contributed to an overall lag in research-based knowledge relative to what is known about adult disorders."	goals: 1) to provide information on children's need for and use of services for mental health reasons, including barriers to mental health care; 2) to provide prevalence and incidence rates of specific mental disorders in child and adolescent populations; and 3) to expand our knowledge of the etiology and development of psychopathology. This project will address a critical public health need for solid, replicated, epidemiologic data on the prevalence of specific mental disorders among community populations of children and youth for mental health planning purposes and will help to attain objectives identified in Healthy People 2000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Authorizing Legislation

	PHS Act/ Other Citation	U.S.Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation...	Section 301	42§241	Indefinite	$500,030,000	Indefinite	$518,256,000
National Institute of Mental Health...	Title IV, Part C	42§285	Such sums as necessary		Such sums as necessary	
National Research Service Awards..........	Section 487(D)	42§288	$400,000,000	26,232,000	Such sums as necessary	26,967,000
Total, Budget Authority.......				$526,262,000		$545,223,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	n/a	n/a	$574,803,000	$583,651,000 2/
1994	$576,015,000	$613,444,000	613,444,000	613,444,000
1995	545,223,000 3/			

n/a = Not applicable.

1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIMH was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $4,723,000, $81,000, and $1,981,000.

3/ The 1995 Request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Extramural research and training..............	---	335,176	---	369,484	---	$385,530	---	$410,616	---	$429,457		+$18,841
Intramural research.........	660	76,385	680	84,543	590	86,993	634	84,862	614	84,936	-20	+74
Research management and support.................	338	27,491	349	30,118	358	31,895	323	30,784	315	30,830	-8	+46
Subtotal, obligations....	998	439,052	1,029	484,145	948	504,418	957	526,262	929	545,223	-28	+18,961
Unobligated balance, lapsing..............	---	195	---	199	---	291	---	---	---	---		
Total, budget authority..	998	439,247	1,029	484,344	948	504,709	957	526,262	929	545,223	-28	+18,961

Justification

National Institute of Mental Health

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
948	$504,709,000	957	$526,262,000	929	$545,223,000	-28	+$18,961,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute of Mental Health. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute of Mental Health (NIMH) is the lead Federal agency for research on mental illness and mental health. The Institute supports and conducts research and research training on the etiology of mental disorders, their treatments, and services. NIMH grantees and scientists seek to understand the entire range of brain and behavioral research from basic science to prevention interventions. A primary goal of NIMH research is to empower the people who are affected by mental illnesses by providing them with improved model therapies and service integration designs that can lead them to independent lives. NIMH's role in the community includes knowledge exchange, professional education, and public information to promote mental health and to destigmatize mental illness.

The wide prevalence of mental disorders has far-reaching effects. In a year, approximately 35.1 million adults 18 and over, or about 22 percent of the adult population are affected by one or more mental disorders, a prevalence rate comparable to that of cardiovascular illness. Fifteen percent of U.S. children and adolescents, more than nine million young people, are affected by a mental, behavioral or developmental disorder, while America's elderly are debilitated by disorders such as Alzheimer's disease and depression. Staggering costs, estimated at $147.8 billion in 1990, are associated with this suffering. Some examples:

- In a one year period, 22.8 million people made 325.9 million ambulatory service visits for mental or addictive disorder treatment.

- Mental health and substance abuse treatments cost U.S. companies $245 per employee in 1991, nearly 10 percent of health care expenses.

- A 1993 study estimates the cost of depression (including manic depression and dysthymia) to be $43.7 billion a year, on par with heart disease. Costs were included for treatment, lost productivity, and loss of life from suicide. The authors estimate that reduced productivity from depression amounts to $3,000 for each depressed worker or $180 for every U.S. employee.

- The annual U.S. spending for anti-depressant medications is $1.1 billion.
- Severe mental illness affects 2.8 percent of the U.S. adult population annually, or approximately five million people. Treatment of these disorders accounts for 25 percent, or $14 billion, of all federal disability payments (Social Security Insurance, SSI and Social Security Disability Insurance, SSDI) annually.

To conquer mental disorders, the NIMH has developed four national research plans: The National Plan for Schizophrenia Research; Approaching the 21st Century: Opportunities for NIMH Neuroscience Research (also called the Decade of the Brain Plan); The National Plan for Research on Child and Adolescent Mental Disorders; and Caring for People With Severe Mental Disorders: A National Plan of Research to Improve Services. Each of these plans serves as a guide for the field, highlighting what is known and what research is needed, while defining areas that warrant major, sustained investment now and in the future.

The President's appropriation request of $545,223,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Mental Health during the last five years has been as follows:

	Amount	FTE
1990	$376,891,000	963
1991	439,247,000	998
1992	484,344,000	1029
1993	504,709,000	948
1994	526,262,000	957

Purpose and Method of Operation

The purpose of NIMH research is to generate new information about the causes, diagnosis, treatment, and prevention of mental disorders. This purpose is accomplished through federal funding of direct intramural research and support for various extramural mechanisms. In addition, NIMH supports research training and career development, and research dissemination.

Overall Budget Policy

The FY 1995 budget request for NIMH is $545,223,000, an increase of $18,961,000, which is 3.6 percent over the comparable 1994 level of $526,262,000. The request includes 929 FTEs, a decrease of 28 from the FY 1994 Appropriation level of 957.

Within the request, funding for research project grants increases by 5.4 percent, from $269,623,000 for 1,230 research project grants in the FY 1994 Appropriation to $284,093,000 for 1,279 research project grants in the FY 1995 President's Budget Request. Continuing grants increase by 7.2 percent, while new and competing grants receive an increase in funding of $876,000, or 1.1 percent, over the FY 1994 Appropriation. Since NIMH is supporting expensive renewal grants resulting in an average cost increase for competing grants of

4.7 percent, NIMH has elected to decrease the number of competing grants from 405 to 391.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a 4 percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. Because of the influx of less expensive grants within the noncompeting component, the noncompeting average cost did not change in FY 1995.

The NIMH total request for research centers is $55,001,000 for 54 centers, a $2,171,000 increase. The Science Education Partnership Awards (SEPA) program has been terminated, for a decrease of two awards. Except for the Minority Institution Research Development Program (MIRDP) grants that will be funded at a 5 percent increase, the budget permits funding the remaining extramural mechanisms with a 2.8 percent increase. The research training mechanism will fund the same number of FTTPs as in FY 1994. Thus, programmatic outputs for other research, research training, and contracts will remain approximately level in the total FY 1995 NIMH budget.

Funding for the NIMH intramural program increases to $84,936,000, which is $74,000 more than the FY 1994 Appropriation of $84,862,000. FTES are reduced by 20, from 634 in FY 1994 to 614 in the President's Budget.

Research management and support is increased to $30,830,000, or $46,000 more than the FY 1994 Appropriation of $30,784,000. FTES are reduced by 8, from 323 in FY 1994 to 315 in the President's Budget.

National Institute of Mental Health

Extramural Research

Authorizing Legislation - Section 301, 487, and Title IV, Part C of the Public Health Service Act. 1995 Authorization: Such Sums as Necessary

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$385,709,000	$410,616,000	$429,457,000	+$18,841,000

To coordinate and conduct its national program of extramural research and research training, NIMH program areas include: the fundamental knowledge base of neuroscience and behavioral science; clinical and treatment research; epidemiology and services research; and prevention research. NIMH also funds extramural research on populations with special mental health needs, including women, racial and ethnic minorities, the homeless, and rural mental health research, as well as AIDS research.

Funding for extramural programs during the last five years has been as follows:

	Amount
1990	$281,351,000
1991	335,252,000
1992	369,509,000
1993	385,709,000
1994	410,616,000

Rationale for the Budget Request

With the FY 1995 extramural request these funds will provide support for the following activities: research and research training, $429,457,000, an increase of $18,841,000 or 4.6% over the over the FY 1994 estimate of $410,616,000. The following are examples of current program activities and future plans.

The Fundamental Knowledge Base of Behavior and the Brain

NIMH is sponsoring the first major report on the current status of the field of behavioral science research since the Institute's return to the National Institutes of Health (NIH) after the reorganization of the Alcohol, Drug Abuse, and Mental Health Administration in FY 1992. The report is intended to be useful, not only within the Institute, but also across the NIH, to more fully inform individuals and organizations about pioneering directions for behavioral research. This report by the Behavioral Science Task Force, sponsored by the National Advisory Mental Health Council, should have a major impact on the future course of behavioral research. Topics of the review include: behavioral development and organization in animals and humans; sensory systems, perception, learning, memory, and motor skills; language and knowledge acquisition, reasoning, problem-solving, judgment; factors that contribute to healthy psychological adjustment across the life-span; factors governing interpersonal relations in families, peer groups, schools and the workplace; and broad social and cultural factors that affect behavior and adaptation.

Brain Biology Relates to Learned Behaviors

In ongoing studies of genetic contributions to behavior, a major breakthrough has been achieved by scientists supported by NIMH in understanding how molecular events translate into learning. The researchers engineered specific mutations in a "knockout" mouse. Mice in which a particular gene form was absent exhibited impaired long-term potentiation (LTP). These mutants also were impaired in their spatial learning and were unable to learn the location of a platform that would enable them to climb out of a pool of water. The link between the missing gene, LTP, and spatial learning is an important piece of information establishing one of the first scientific links between a specific gene, its function within the cell, and the individual aspect of mammalian behavior (spatial learning and memory) that it governs.

Neuroimaging

Scientists now have a number of neuroimaging techniques to examine brain activity in living subjects. These approaches include positron emission tomography, single photon emission spectroscopy, magnetic resonance imaging (MRI, including a new "FAST MRI"), magnetic resonance spectroscopy, magneto-encephalography, and brain electrical activity mapping. For example, NIMH-sponsored investigators are using MRI to study gross structural changes in the brain and found that the hippocampal region was smaller in persons with schizophrenia than in normal control subjects. The amount of reduction in size correlated with the severity of positive symptoms. Another research team used PET to track brain glucose metabolism in unmedicated schizophrenic patients. Decreased metabolism in the medial frontal cortex correlated strongly with the severity of negative symptoms, suggesting that this region may be tied to schizophrenic pathology. Finding such differences with imaging techniques is particularly timely because developmental studies have also pinpointed these areas as playing important roles in the pathogenesis of schizophrenia.

The Human Brain Project

Understanding brain function requires the integration of information from the level of the gene to the level of behavior. At every level there has been an explosion of information with concomitant, and increasing specialization of scientists. The price of this progress and specialization is that it is becoming virtually impossible for any individual researcher to maintain an integrated view of the brain. The Human Brain Project is a broad-based, long-term research initiative which supports research and development of advanced technologies to open information superhighways to neuroscientists and behavioral scientists, and to provide an information infrastructure for the neurosciences of the 21st century. These technologies include computer databases of neuroscience information, network systems, and associated tools that will allow information to be shared, integrated and synthesized. The databases will be used to establish norms of cellular, circuitry, and neurochemical information that will serve to detect and define experimental and pathological variations. This project has been enthusiastically endorsed by the Institute of Medicine. Pilot studies are now underway along with a new program announcement, "The Human Brain project: Phase I Feasibility Studies". The five-year "Phase I" effort will support the development of technologies to acquire, store, manage, analyze, integrate and disseminate neuroscience information. A goal is to promote communication and collaboration across scientific disciplines and geographic locations.

Depression, Mood Disorders

Nearly 18 million Americans--9.5 percent of the adult population--experience one or more affective disorders over the course of a year. Affective disorders, also called mood disorders and depression, are recurrent, often life-time battles. Women are 1.7 times more likely to experience an episode of depression during their lives than men. Studies by NIMH researchers are helping to explain the higher rates of depression and dysthymia found in women. For example, NIMH research has implicated several neurotransmitter systems in the pathophysiology of depression and has shown that gender differences exist. Most recently, these studies have accumulated evidence suggesting that there may be gender differences in how these neurotransmitter systems change with age. One preliminary study has found, for example, that the functioning of some serotonergic systems appears to change with age in women but not in men. Such differences may play a role in determining vulnerability to and expression of depression in men and women.

Schizophrenia

A new medication, risperidone, significantly extends the treatment options for this mental disorder and improves the ability of mental health care providers to use pharmacotherapy in the most effective and least toxic manner. Schizophrenia, the most chronic and disabling of the severe mental disorders, strikes young adults with tragic consequences for both patients and families. Currently available medications are associated with severe side effects, such as tardive dyskinesia. On the other hand, the newly marketed antipsychotic drug clozapine, although it appears to be free from these effects, carries the risk for a life-threatening blood disorder, agranulocytosis, as well as seizures. This toxicity and the necessity for weekly monitoring of blood has made this medication extremely expensive and limited its usefulness. Experience with a new generation of medications will also help refine the search for even better drugs and increase our understanding of the causes of schizophrenia.

Children and Adolescents

Research on mental disorders in children and adolescents, which is guided by the National Plan for Research on Child and Adolescent Mental Disorders, is a high priority at NIMH. The disorders in childhood and adolescence produce a wide array of repercussions that vary in severity, duration, complexity, and implications for an individual child's future. Virtually, all of the major mental disorders begin sometime in childhood or adolescence, and even when the disorders do not persist into adulthood, they can profoundly affect psychological and social development. Mental disorders can impair children's cognitive function, such as their ability to reason or learn, and affect emotional adjustment, leading to depression or anxiety disorders. There may also be extreme disruptions in behavior. The ordinary changes of childhood--growth and development--present a background of fluctuations that complicate diagnoses and treatments. Clinical investigators are studying the first onset of disorders as an opportunity to prevent progression and the enduring consequences. Researchers also need to gain a better picture of the antecedents, course, and outcome of mental disorders in this population. Two recent examples of new directions include:

- Adolescent depression occurs at a crucial time, influencing future adjustment and substantially increasing the risk for future episodes of depression. An NIMH-funded study has recently found that 9.6 percent of a sample of 1700 entering high school students, coming from a wide cross section of ethnic and socioeconomic backgrounds, met the diagnostic criteria for depression. One in nine students had experienced two or more episodes, and relapse rates approached 20 percent.

- Several longitudinal studies funded by NIMH have found that even in high risk families--in which both parents have a mental disorder, where there is a strong family history of illness, and chaotic family life--some children remain free from the affects of mental disorders. Researchers call these children resilient. As a group, these children were found to create a repertoire of coping skills early in their lives. Resilience may have both psychological and biological components and has important implications for prevention research.

Mental Illness in Older People

NIMH research is working toward an improved understanding of the etiology, course and treatment of the major mental disorders of late life. At least 8 percent of the elderly population are affected by senile dementias, including Alzheimer's disease; 20 percent suffer from anxiety disorders including phobic disorders; and nearly 1 percent suffer from schizophrenia. Delirium, sleep disorders, and personality disorders are also common. Nearly 40 percent of geriatric patients having major depression also meet criteria for anxiety disorder. As many as 30 percent of dementia patients also suffer from major depression, and can exhibit symptoms of agitation, paranoia, hallucinations, and sleep disturbance. Among the frail elderly with multiple coexisting medical illnesses, "failure to thrive" has been associated with psychiatric symptoms. By one estimate, only about 10 percent of the elderly who need psychiatric treatment ever receive it.

Elderly Americans have the highest rates of depressive symptoms among all age groups; major depression affects as many as one million people age 65 and over. A study found that 12.6 percent of nursing home patients had major depression and 18.1 percent had depressive symptoms. Most of these cases had gone unrecognized and untreated. Depressed elderly people are more likely to use health care services for physical problems, and there is an increased risk of suicide, particularly among elderly white men, whose suicide rate is over twice that of adolescent males. With 1.6 million elderly Americans residing in nursing homes, detecting and treating depression in the elderly could have a significant impact on the health and well-being of older Americans and on the cost of caring for them. An NIMH-supported study demonstrated that elderly patients who are prone to recurring depressions can be treated successfully with a combination of the antidepressant medication nortriptyline, psychotherapy, and family support groups. In this study, 79 percent of those receiving treatment for 16 weeks achieved a full clinical remission of their depressive symptoms.

Services Research

A major problem for mentally ill people is fragmentation of services. Moreover, health care reform will require developing a knowledge base of integrated approaches to treatment and services for people with severe mental disorders, especially those outside traditional systems of care. NIMH is continuing to expand its support for mental health services research with the goals of improving the organization, financing, quality, accessibility, delivery, outcomes, and cost-effectiveness of these services. Building on the results of work already accomplished, NIMH is embarking on a broad-based strategy for bringing the full power of scientific research into its ongoing effort to find ways to improve services and ultimately the quality of life for persons stricken with mental illnesses. Through this greatly increased effort, NIMH also aims to increase the store of scientific knowledge which will aid policy makers and the public to accomplish national health care reform.

Clinical trials of a care model demonstrate that Programs of Assertive Community Treatment (PACT) yield better patient outcomes than standard community treatment with no greater cost. The PACT model uses a treatment team approach to provide a full range of medical, psychosocial, and rehabilitation services, to offer crisis intervention, formal education, community resource management, direct skills training, and employment assistance. PACT is the only community-based services program for people with severe mental illnesses that has been tested in multiple clinical trials. Compared with patients receiving more conventional treatment, those participating in PACT programs have lower rates of hospitalization and increased independent living, employment, and social interactions. Cost-benefit analyses show that the benefits of the program significantly outweigh the treatment costs. The PACT model has now been implemented State-wide in Delaware, Michigan, Rhode Island, and Wisconsin, and on a more limited basis in an additional 20 States. Ongoing research is examining variability in implementation of the PACT model and the application of the program for subgroups of patients by diagnosis, gender, and ethnic background. This is an innovative example of how research can influence health care service delivery.

Prevention

Developing the knowledge necessary to prevent mental illness would represent the ultimate achievement of NIMH biomedical and behavioral research.

NIMH's prevention research agenda seeks to provide basic concepts to support the core of prevention science; to identify effective, innovative methods and techniques; and to support substantive, methodological, and integrative research programs and research training for the scientists in this specialized field. In FY 1995, NIMH has a unique opportunity to expand on the prevention research base and develop new approaches for intervention due to the renewed concentration on prevention efforts resulting from the healthcare reform agenda. As America attempts to turn its current system from one focused on "medical" care to one focused on "health" care, prevention of disease and disorder takes on new meaning and value.

NIMH plans five specially designed efforts that will direct the evolution of prevention strategies: (1) to determine the prevalence, risk factors, protective factors, disease course, long-term consequences, and service use needs of children and adolescents with mental disorders; (2) to advance understanding of the biological and behavioral determinants for eating disorders and depression, including gender differences; (3) to develop a long-term, coordinated program targeted at multiple risk, protective, and resiliency factors for the prevention of child abuse and neglect and the lasting psychological and social damage to children that may result; (4) to develop and evaluate strategies to prevent violence against women and to ameliorate the effects of violence on women, which have been linked to women's mental disorders such as posttraumatic stress disorder, depression, and anxiety disorders; and, (5) to determine genetic and environmental risks and protective factors, along with a focus on preventing recurrence, deterioration, and morbidity of severe mental disorders.

Health and Behavior

The brain influences and regulates body functions, including the immune system, digestive functions, the endocrine system, and the circulatory system. Because of this interrelationship, psychological factors and therapies have an important role to play in the onset and treatment for physical illnesses. Rapidly accumulating findings underscore the importance--for clinical outcomes as well as health care cost considerations--of accurately identifying and appropriately treating comorbid physical illnesses and mental disorders. Recent research has shown, for example, that approximately 25 percent of heart attack survivors suffer from clinical depression and when a depressive illness follows a heart attack, the time required for recovery is double that for other patients. New antidepressants which do not interact with the heart can dramatically shorten overall recovery time.

Importantly, an analysis sponsored by the National Advisory Mental Health Council for the Senate Appropriations Committee estimated that appropriate and timely treatment of severe mental disorders would produce a 10 percent reduction in the cost and use of general medical services by people with severe mental disorders.

Aggressive and Violent Behaviors

NIMH research examines the mental health aspects of aggression and traumatic stress, focusing on perpetrators of violence; victims; the legal system of criminal and civil commitment; and a program of emergency research, studying disaster, combat, community violence, and terrorism.

Violence among our nation's children has become a pressing national concern in recent years. An estimated two to four percent of children display some signs of aggressive behavior. Boys with abnormally aggressive behavior outnumber girls three-to-one. Conduct disorder, a particularly severe manifestation of aggressive behavior, progresses to the adult condition of antisocial personality disorder in about a third of all cases, and virtually all adults with antisocial personality disorder had conduct disorder as children. In addition, childhood problems with aggressive behavior increases the risk for developing other disorders in adulthood, including substance abuse, obsessive-compulsive disorder and schizophrenia. The causes of these problems are not known, but NIMH-supported research is attempting to find those factors that lead to problems of aggressive behavior.

New findings from NIMH-funded research are compelling a reinterpretation of the prevailing view that date and acquaintance assault is the consequence of miscommunication between dating partners. Although a survey of women college students found that nearly 13 percent were sexual assault victims during their first year in college, the single best predictor of this was adolescent sexual assault, and the best predictor of adolescent victimization was childhood victimization. The data clearly indicate that waiting until college to begin "date rape prevention" programs is too late for significant numbers of women. A companion study of freshmen men, meanwhile, found that university males who are sexually, physically or dually assaultive toward their female companions are also apt to be assaultive in general, to use weapons, damage property, commit theft, and engage in rowdy and publicly drunken behavior. Furthermore, precollege involvement in both sexually and physically assaultive violence was the single best predictor of later dating violence. These findings imply strongly that rape prevention programs must target assaultive males, and they must do so early in a young man's life.

Cross-cutting Issues: Populations with Special Mental Health Needs

Women's Mental Health Issues

Research questions related to the risks for, prevalence of, and treatment of mental disorders in women have been an important part of NIMH's scientific agenda. Valuable information has been gained about the implications of biologic factors in understanding the causes of, and in developing treatments for mental illness. An estimated 6 percent of U.S. women, in contrast to 3 percent of men, will experience a major depression in their lifetime. At least another 6 percent of women have dysthymia, a less severe but often more chronic form of depression. Schizophrenia in women appears to be marked by differences in manifestations and course. Anxiety, panic, and phobic disorders also predominate in women, affecting two to three times as many women as men. Eating disorders, which may be related to obsessive-compulsive disorder, are found almost exclusively in women. NIMH has a large portfolio of research focused on women's mental health and disorders.

Medical science has found that early-stage breast cancer can be successfully treated by either mastectomy or lumpectomy. Many women choose lumpectomy believing that conservation of their breast will result in less psychological trauma. However, NIMH researchers have recently found that in the long run the mental health effects of lumpectomy versus mastectomy surgical procedures may be equal. Both surgical groups experienced a lessening of psychosocial distress during the first 15 months following surgery. In the short run, however, patients receiving lumpectomies, especially younger ones, experienced less emotional support. This is a grave concern for this population because emotional support often serves as a buffer to stress caused by this surgical procedure. These findings underline the importance of greater social support for younger breast conservation patients during the early stages of recovery.

Rural Populations

Efforts to provide mental health services in rural areas are impeded by a number of interrelated problems. The large distances to travel and rural poverty make access to services difficult and expensive and make it hard to attract sufficient numbers of mental health service providers. These factors have an effect on the quality of service provided and on the use of services by those in need. NIMH encourages research on rural problems through a special announcement and has funded three rural research centers. Three more centers with primary foci on service provision or youth behavior also concentrate on rural populations. NIMH is supporting a contract to produce a report on the current state of Mental Health and Rural America: 1980-1993. This report, in press, will guide potential rural researchers toward high priority topics. The report documents that one of the serious difficulties in meeting mental health problems in rural America continues to be the lack of qualified mental health service providers.

Racially- and Ethnically-Defined Populations

Epidemiologic data show that there are no racial differences in the prevalence of most mental disorders. However, recent empirical studies, many of which have been carried out in NIMH-supported Minority Research Centers, are confirming cultural differences in the expression of symptoms, resulting in misdiagnoses and inappropriate treatment. NIMH also is sponsoring studies of ethnically-defined populations as they respond to psychoactive drugs. NIMH recently contributed to the development of guidelines on the effect of culture on the expression of mental disorders to be included in the new American Psychiatric Association's Diagnostic and Statistical Manual, DSM-IV.

Despite a number of studies that have shown high rates of depressive disorders and alcohol abuse among American Indians, current research has not yet clarified the role of comorbidity in the psychopathology found in this population. NIMH researchers at the Flathead Reservation using a study design that emphasized the importance of Indian culture, found that behaviors the tribe valued as signs of maturity and spirituality may masquerade as depressive symptoms to an outside observer and may not always indicate real psychological distress. Drinking also may be viewed as a positive expression of sociality and kinship. Suicide is a risk only when feelings of worthlessness are present. Young men, in contrast to older men in this population, were especially susceptible to feelings of worthlessness and severe problem drinking. These results facilitate culturally appropriate diagnosis and effective identification of persons at risk.

The Institute supports a range of training opportunities. The Minority Fellowship Program for graduate students is designed to ensure that minority investigators assume a prominent position in research. The NIMH Career Opportunities for Research (COR) honors program provides support to college undergraduates. The Minority Institutions Research Development Program (MIRDP) aims to increase the capacity of predominantly minority institutions, and enhance the capability of their faculty, to conduct rigorous research. NIMH also has been strengthening its ties to Historically Black Colleges and Universities (HBCU) to encourage mental health and behavioral research. A special effort is being directed to schools of medicine as a base for mental health research in these populations. The Minority Dissertation Grant program has been conceived as a way to increase the number of Ph.D.s being awarded to students in these populations. The Institute hopes to fund approximately 10 of these awards a year in any area of relevant research. Among other accomplishments this year, NIMH funded the first regular research training grant at an HBCU for pre- and post-doctoral students.

Homelessness and Mental Illness

Perhaps no group of disabled people in the United States is as impoverished and as alienated from assistance as the homeless mentally ill population. About one-third of the homeless population is estimated to have severe psychotic disorders such as schizophrenia, severe depression, manic-depressive disorder, or paranoia. Homeless women generally face the same social and economic problems as do men, but in an intensified form due to the social marginalization of women and the responsibilities of parenthood, often borne by women alone. An alarming number of these women have been physically and sexually abused as children as well as in adulthood; many have mental disorders and substance abuse problems. These problems are frequently compounded for women of color. NIMH supports a substantial portfolio of state-of-the-art research on mental illness and homelessness.

Research Training

The NIMH National Plans identified the need to train the next generation of scientists. The Institute continues to sponsor a full range of training mechanisms to foster young talent. In FY 1994, NIMH began a new program, the B/START, or "Behavioral Science Track Award for Rapid Transition". These awards are small ($25,000 in direct costs) for exploratory projects of newly independent investigators. NIMH has developed the Research Infrastructure Support Program (RISP) to enable institutions with relatively small but viable research programs to develop into major mental health research settings. The NIMH Research Training and Development Newsletter was introduced as a means to inform the Institute staff of changes to the mechanisms of research training and career development and the ongoing formulation of NIH policy concerning these mechanisms. The first issue was circulated in October 1993.

National Institute of Mental Health

Intramural Research

Authorizing Legislation - Section 301, 487, and Title IV, Part C of the Public Health Service Act. 1995 Authorization: Such Sums as Necessary

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
590	$87,020,000	634	$84,862,000	614	$84,936,000	-20	+$74,000

The NIMH Intramural Research Program (IRP) plans and administers a comprehensive long-term research program dealing with the causes, diagnosis, treatment, and prevention of mental disorders, as well as the biological and psychosocial factors that determine human behavior and development. The IRP consists of approximately 400 investigators and operates 23 laboratories and clinical branches on the campus of the National Institutes of Health, at the Poolesville Animal Facilities, and at the Neuropsychiatric Research Hospital on the campus of Saint Elizabeth's Hospital in Washington, D.C. Several hundred active research projects in the basic neurosciences, clinical pharmacology, clinical psychiatry, and behavioral sciences are conducted in these facilities each year. The IRP scientists provide a critical link between basic and applied mental disorder research. The IRP is currently in a period of stringent evaluation to redefine the program and its goals.

The IRP is developing a growing partnership with industry. Stimulated by the Federal Technology Transfer Act of 1986, the IRP scientists have had a steadily increasing number of collaborations with industry based on their inventions. Ten Cooperative Research and Development Agreements (CRADAs) were active in FY 1993. Eleven new patents were filed, and five new patents were issued.

Funding for Intramural Research during the last five years has been as follows:

	Amount	FTE
1990	$68,776,000	644
1991	76,488,000	660
1992	84,564,000	680
1993	87,020,000	590
1994	84,862,000	634

Rationale for the Budget Request

The FY 1995 request for Intramural research is $84,936,000, an increase of $74,000 over the FY 1994 level. Some examples of ongoing research and plans for FY 1995 include:

The hormones vasopressin and oxytocin affect learning, memory, maternal and sexual behavior, water retention, thermoregulation, cardiovascular function, and the response to stress. NIMH intramural scientists have cloned the genes that encode three vasopressin and one oxytocin receptor, which may be responsible for many of the hormones' actions. One of the vasopressin receptors--the V2 subtype--mediates the peptide's antidiuretic action. It is thought that the disease hereditary nephrogenic diabetes insipidus (NDI) arises from a defect in the gene encoding this receptor. Untreated, the condition can cause severe dehydration, growth retardation, and mental retardation. The intramural investigators showed that the V2 vasopressin receptor gene is localized close to the locus for NDI on the X chromosome. They have subsequently shown that in one NDI family, a mutation in the V2 receptor leads to a defective receptor protein which would not bind vasopressin. Other groups worldwide have found different V2 receptor mutations associated with the disease in separate families. Identification of the disease locus allows rapid detection of the mutant gene in female carriers and permits the appropriate counseling regarding the rearing of male children. In the long term it may be possible to 'cure' the disease by replacing the defective gene with the normal one through gene therapy.

Studies of obsessive compulsive disorder (OCD) and related illnesses have grown to include Sydenham's chorea, a variant of rheumatic fever. Systematic evaluation of children with Sydenham's chorea by NIMH intramural scientists revealed that 75% had the abrupt onset of OC symptoms concomitant with the onset of their movement disorder. Antineuronal antibody measurements in these children, and a subgroup of children with primary OCD or Tourette's disorder, were positive during symptom exacerbations. Magnetic resonance imaging in acutely ill children revealed enlarged caudate nuclei which decreased to normal size following symptom remission. Acutely ill patients with either Sydenham's chorea or OCD have been treated with either plasma exchange, intravenous immunoglobulin, or prednisone. Pilot data have been encouraging as dramatic reductions in both motoric and psychiatric symptoms were observed. OCD is a common, debilitating mental illness, and medical models, such as that hypothesized in Sydenham's chorea, may provide insights into the etiology of this troublesome disorder. If a subgroup of patients can be identified who are at genetic, developmental, or neuroimmunologic risk, effective intervention and even prevention strategies may be devised.

NIMH intramural scientists are continuing their innovative work on Gaucher's disease. Previous achievements included making a transgenic mouse model of Gaucher disease by replacing the normal mouse gene with a defective gene. These mutant mice have symptoms and pathology analogous to what is observed in the severe human neonatal type. IRP researchers are currently generating transgenic mice having milder forms of this human inherited metabolic disease, that affects approximately 10,000-20,000 Americans of primarily Eastern European Jewish ancestry. Treatment requires expensive enzyme infusions, costing $100,000 to $400,000 annually. In FY 1994, the IRP in collaboration with Enzon, Inc., plans clinical trials of enzyme replacement for Gaucher disease using a polyethylene glycol (PEG) modified enzyme. The Phase I trial will study pharmacokinetics, pharmacodynamics, and safety of the new drug, which will be administered by injections and at lower dose than the currently available enzyme. Current research also focuses on recombinant production of active proteins for therapeutic use in the milk of transgenic animals, including genetically modified farm animals, such as pigs. This work is intended to result in more efficient and cost effective methods for producing proteins which can be applied to therapy for many diseases.

For nearly twenty years it has been believed that visual memories are stored in the cerebral cortex as a result of enabling actions of the limbic system, including the amygdala and hippocampus. NIMH intramural scientists have now discovered that the critical structure for enabling memory storage is actually the rhinal cortex. This region underlies the amygdala and hippocampus and is frequently involved when the latter structures are damaged or in disease or trauma. Recent results show that damage to the rhinal cortex that spares the amygdala and hippocampus is sufficient to produce a severe anterograde amnesia. Based on this new knowledge the investigators have focused their electrophysiological studies on this region in primates. These studies have revealed several neural mechanisms that could provide a basis for recognition memory.

National Institute of Mental Health

Research Management and Support

Authorizing Legislation - Section 301, 487, and Title IV, Part C of the Public Health Service Act. 1995 Authorization: Such Sums as Necessary

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
358	$31,980,000	323	$30,784,000	315	$30,830,000	-8	+$46,000

This activity provides staff and resources for the administrative management and scientific direction of the Institute. Managerial and administrative services are provided through the following organizational components: The Office of the Director, the Office of Equal Employment Opportunity, the Office of Legislative Analysis and Coordination, the Office of Scientific Information, the Office of Resource Management, and the Office of Program Planning and Science Policy. The Office of the Director includes the administration and financial management programs of the Institute. Scientific direction and administrative management of the Institute's extramural review and oversight is provided by the Division of Extramural Activities. This activity includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of their program's research grant, contract and training programs.

Funding for the Research Management and Support program during the last five years has been as follows:

	Amount	FTE
1990	$26,764,000	319
1991	27,507,000	338
1992	30,271,000	349
1993	31,980,000	358
1994	30,784,000	323

Rationale for the Budget Request

The FY 1995 request for Research Management and Support is $30,830,000 and 315 FTEs. This represents an increases of $46,000 and a decrease of 8 FTEs from the FY 1994 Appropriation of $30,784,000 and 323 FTEs.

NIMH's publications program provides a link between the research community and the public whose tax dollars support our programs. Messages designed to combat stigma are an important part of this program. Among new titles for the public: Eating Disorders (NIH 93-3477) tells how anorexia and bulimia afflict at least 3% of girls and young adult women in the U.S. and describes symptoms and alternatives. Learning Disabilities (NIH 93-3611) provides up-to-date information on learning disabilities and the role of NIMH-sponsored research in discovering underlying causes and effective treatments. It also describes treatment options, strategies for coping, and sources of information and support. As part of its knowledge exchange activities, NIMH has released: Special Report: Schizophrenia (NIH 93-3499); AIDS Research: AN NIMH Blueprint for the Second Decade (NIH 93-3563); and the Fourth Report of the Advisory Panel on Alzheimer's Disease (NIH 93-3520).

Approximately 2.4 million Americans have panic disorder. As part of its ongoing three-year panic disorder education effort, a new pamphlet was produced in both English and Spanish along with a bookmark, a fact sheet, a resource list and a guide for primary care physicians. NIMH inaugurated a new hotline, 1-800-64-PANIC offering information about panic disorder to healthcare providers and the general public. New and reprinted titles about panic disorder were added: Panic Disorder Referral List, (OM 00-4098), is a list of organizations that provide guidance about locating mental health treatment professionals, self-help groups, and other resources for people with panic disorder. Panic Disorder Resource List, revised 1993 (OM 00-4078), is a list of books, pamphlets, scientific articles, and videotapes available from several sources. Understanding Panic Disorder, reprinted 1993, (NIH 93-3509), describes in detail the symptoms of panic attacks, strategies for coping with panic, and treatments--including cognitive-behavioral therapy, therapy with medications, and combinations of more than one type of treatment. Especially useful for family members is a list of tips for helping the person with panic disorder. Panic Disorder in the Medical Setting (NIH 93-3482) was reprinted in 1993 for professionals dealing with this disorder.

As a result of an increased interest in NIMH publications, public and provider requests doubled to the Federal Government's Consumer Information Center in Pueblo, Colorado. The Center promotes and distributes many NIMH publications, as does the Government Printing Office. The NIMH pamphlets You Are Not Alone (ADM-92-1178), Alzheimer's Disease (ADM-92-1696), and What To Do When A Friend Is Depressed (ADM-92-1628) are among the most frequently requested of all publications from the Government.

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	9	8	8
Office of Prevention	6	5	5
Office on Equal Employment Opportunity	2	2	2
Office of Rural Mental Health Research	1	1	1
Office for Special Populations	5	5	4
Office on AIDS	12	12	12
Office of Legislative Analysis and Coordination	5	5	4
Office of Scientific Information	24	21	20
Office of Resource Management	76	74	72
Office of Science Policy and Program Planning	15	13	12
Division of Neuroscience and Behavioral Science	33	30	29
Division of Clinical and Treatment Research	58	49	49
Division of Epidemiology and Services Research	60	51	51
Division of Extramural Activities	52	47	46
Division of Intramural Research Programs	590	634	614
Total	948	957	929

Average GM/GS Grade	
1990	10.4
1991	10.3
1992	10.2
1993	10.2
1994	10.2

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

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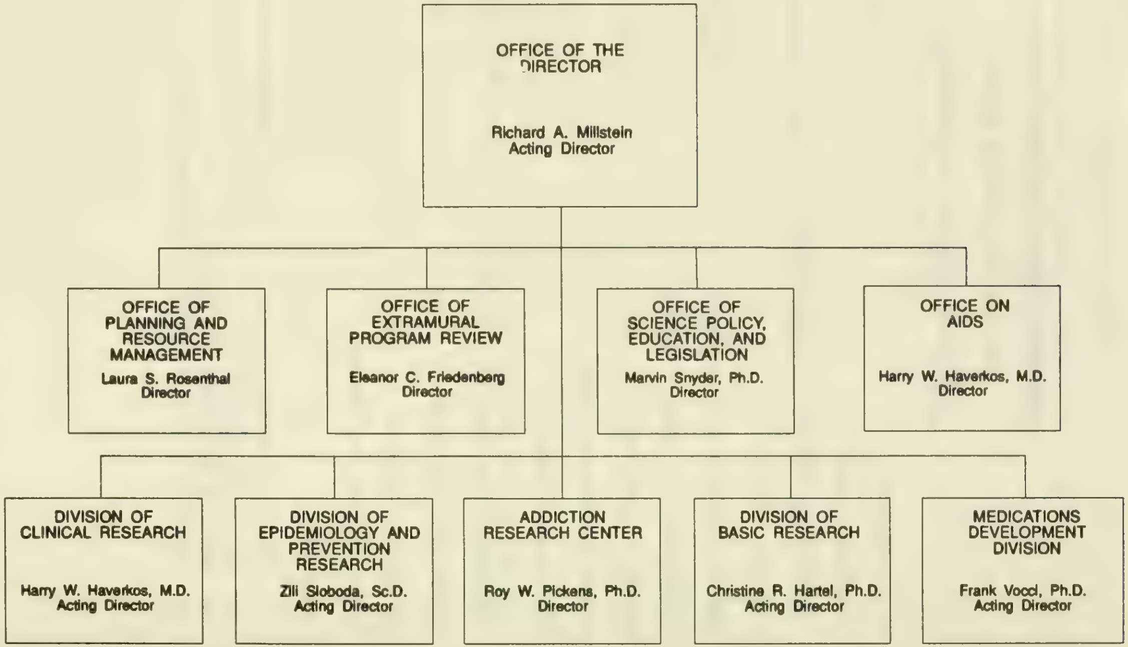
NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

For carrying out section 301 and title IV of the Public Health Service Act with respect to drug abuse, [$425,201,000] *$291,963,000 of which $4,645,000 shall not become available for obligation until September 19, 1995.* (Departments of Labor, Health, and Human Services, and Education, and Related Agencies Appropriations Act, 1994.)

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Language Analysis

Language Provision	Explanation
". . . of which $4,645,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation................	$408,982,000	$425,201,000	$291,963,000
Section 511 0.8% reduction...	-3,272,000		
Section 513 consultant services reduction.........	-430,000		
Section 216 S & E reduction..	-1,474,000		
Subtotal, adjusted appropriation............	403,806,000	425,201,000	291,963,000
Real transfer from other NIH accounts for tuberculosis research......	+377,000		
Comparative transfer to the Office of AIDS Research, NIH for HIV activities......	-127,047,000	-143,376,000	
Subtotal, adjusted budget authority.........	277,136,000	281,825,000	291,963,000
Unobligated balance, lapsing.	-94,000		
Total, obligations.........	277,042,000	281,825,000	291,963,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1993 -- $5,262,000 and 1 FTE; 1994 -- $5,262,000 and 1 FTE; 1995 -- $5,262,000 and 1 FTE.

Note: Excludes $20,000 for royalties received in FY 1993 and $15,000 in FY 1994.

NATIONAL INSTITUTES OF HEALTH
National Institute on Drug Abuse

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	430	$116,655,000	447	$128,661,000	388	$110,311,000
Admin. supplementals	(13)	353,000	(12)	428,000	(12)	446,000
Competing						
Renewal	85	25,286,000	67	21,863,000	97	37,078,000
New	93	20,445,000	67	14,456,000	96	22,848,000
Subtotal, competing	178	45,731,000	134	36,319,000	193	59,926,000
Subtotal, res projects	608	162,739,000	581	165,408,000	581	170,683,000
Research centers						
Specialized/comprehensive	19	20,827,000	19	23,254,000	19	25,292,000
RCMI		32,000				
Subtotal, centers	19	20,859,000	19	23,254,000	19	25,292,000
Other research						
Research career program	65	6,253,000	68	6,800,000	68	7,079,000
Cooperative clinical res	2	2,316,000	3	2,174,000	2	1,467,000
Other research related	51	4,495,000	48	3,936,000	50	6,393,000
Subtotal, other res	118	13,064,000	119	12,910,000	120	14,939,000
Total, research grants	745	196,662,000	719	201,572,000	720	210,914,000

Training:						
Individual awards						
Noncompeting..............	41	677,000	42	844,000	43	929,000
Competing.................	23	545,000	25	502,000	24	518,000
Subtotal, individual.....	64	1,222,000	67	1,346,000	67	1,447,000
Institutional awards						
Noncompeting..............	160	4,431,000	164	4,667,000	164	4,910,000
Competing.................	29	501,000	25	447,000	25	471,000
Subtotal, institutional..	189	4,932,000	189	5,114,000	189	5,381,000
Total, training..........	253	6,154,000	256	6,460,000	256	6,828,000
Research and development contracts.................	77	31,146,000	57	30,600,000	57	30,600,000
	FTEs		FTEs		FTEs	
Intramural research..........	137	18,687,000	114	18,686,000	108	18,678,000
Res management and support...	287	24,487,000	287	24,507,000	282	24,943,000
Total....................	424	277,136,000	401	281,825,000	390	291,963,000
(Clinical Trials)		(42,753,000)		(45,800,000)		(47,300,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTE OF HEALTH
National Institute on Drug Abuse
Summary of Changes

1994	Estimated budget authority	$281,825,000
1995	Estimated budget authority	291,963,000
	Net change	+10,138,000

Changes:	1994 Current Estimate Base FTE	1994 Current Estimate Base Budget Authority	Change from Base FTE	Change from Base Budget Authority
A. Built-in:				
1. Intramural				
a. Within grade increase		$7,269,000		+$87,000
b. One less day of pay				
c. Annualization of		7,269,000		-24,000
January 1994 locality pay		7,269,000		+67,000
d. January 1995 pay increase		7,269,000		+87,000
e. Centrally furnished svcs		49,000		+2,000
f. Service and supply fund increase		5,714,000		+160,000
g. Increased cost of laboratory supplies, materials and other expenses		11,368,000		+190,000
Subtotal				+569,000
2. Research Management & Support				
a. Within grade increase		$14,729,000		+201,000
b. One less day of pay		14,729,000		-56,000
c. Annualization of January 1994 locality pay		14,729,000		+113,000
d. January 1995 pay increase		14,729,000		+177,000
e. Federal employees compensation fund, unemployment compensation		117,000		+17,000
f. Centrally furnished svcs		317,000		+13,000
g. DHHS Working Capital Fund		347,000		+3,000
h. Federal telecommunications system increase		430,000		+6,000
i. Service and supply fund increase		5,786,000		+162,000
j. Increased cost of laboratory supplies, materials and other expenses		9,461,000		+195,000
Subtotal				+831,000

Summary of Changes -- con't

	1994 Current Estimate Base		Change from Base	
	FTE	Budget Authority	FTE	Budget Authority
B. Program:	No.	Amount	No.	Amount
1. Research project grants				
a. Noncompeting.............	447	129,089,000	-59	-18,332,000
b. Competing................	134	36,319,000	+59	+23,607,000
Subtotal...................	581	165,408,000	0	+5,275,000
2. Research centers..............		23,254,000		+2,038,000
3. Other research................	119	12,910,000	+1	+2,029,000
Total, research grants......	700	201,572,000	+1	+9,342,000
4. Training......................	256	6,460,000		+368,000
	FTE		FTE	
5. Intramural research	114	18,686,000	-6	-577,000
6. Research management & support.	287	24,507,000	-5	-395,000
Subtotal.................				+8,738,000
Total changes				+10,138,000

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NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment...	401	390	-11
Full-time equivalent of overtime and holiday hours......	2	2	---
Average ES salary..................	$108,200	$109,300	+1,100
Average GM/GS grade................	10.9	10.7	-0.2
Average GM/GS salary...............	$49,300	$49,900	+600
Average salary, grades est by act of July 1, 1944 (42 USC 207).........	$55,300	$56,000	+700
Average salary of ungraded positions	$111,800	$113,100	+1,300
Personnel compensation:			
Full-time permanent..............	$14,103,000	$14,115,000	+12,000
Other than full-time permanent....	2,566,000	2,540,000	-26,000
Other personnel compensation......	428,000	420,000	-8,000
Special personnel services........	919,000	893,000	-26,000
Subtotal, personnel compensation.	18,016,000	17,968,000	-48,000
Personnel benefits.................	3,965,000	3,965,000	----
Benefits for former personnel.......	17,000	17,000	----
Travel and transportation of persons	480,000	480,000	----
Transportation of things...........	63,000	63,000	----

	1994 Appropriation	1995 Estimate	Increase or Decrease
Rental payments to GSA	700,000	770,000	+$70,000
Communications, Utilities and miscellaneous charges	1,588,000	1,652,000	+64,000
Printing and reproduction	553,000	544,000	-9,000
Other Services:			
Consultant Services	3,585,000	3,730,000	+145,000
Other Services	3,512,000	2,498,000	-1,014,000
Purchases from Govt. Accounts	11,851,000	13,548,000	+1,697,000
R&D Contracts	25,546,000	25,546,000	----
Supplies and materials	1,205,000	1,205,000	----
Equipment	2,712,000	2,235,000	-477,000
Grants, subsidies and contributions	208,032,000	217,742,000	+9,710,000
Total	281,825,000	291,963,000	+10,138,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these activities are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIDA

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	14,103	14,103	14,115	12
11.3	Other than full-time permanent	2,566	2,566	2,540	(26)
11.5	Other personnel compensation	428	428	420	(8)
11.8	Special personnel services payments	919	919	893	(26)
11.9	Subtotal, personnel compensation	18,016	18,016	17,968	(48)
12.1	Civilian personnel benefits	3,965	3,965	3,965	0
13.0	Benefits for former personnel	17	17	17	0
	Subtotal Pay Costs	21,998	21,998	21,950	(48)
21.0	Travel and transportation of persons	480	480	480	0
22.0	Transportation of things	63	63	63	0
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	3,000	1,588	1,652	64
24.0	Printing and reproduction	690	553	544	(9)
25.0	Other Services	12,160	11,934	12,895	961
26.0	Supplies and materials	2,290	1,205	1,205	0
	Subtotal non-pay costs	18,683	15,823	16,839	1,016
	Total Administrative Costs	40,681	37,821	38,789	968

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1994 House Report	
Multidisciplinary Research Centers	
1. The House in its report 103-156, page 67, stated: "... the Committee supports development of new comprehensive research mechanisms to demonstrate the effectiveness of centrally-coordinated service and research programs that are focused on populations of women, children, and minorities."	1. In October 1993, NIDA issued a Request for Applications for establishment of Drug Dependence Research Centers to provide a stable environment for coordinated research on the efficacy of behavioral and pharmacologic treatment services. While the primary function of these centers will be the conduct of high quality interdisciplinary research, the provision of services and the training of personnel will be integral to the research effort. Special emphasis will be placed on the inclusion of women, children, minorities, and the underserved.
1994 Senate Report	
Substance Abuse Centers	
1. The Senate in its report 103-143, page 113, stated: "It is the Committee's intention that NIDA support up to 5 multidisciplinary comprehensive substance abuse training, service, and research centers to demonstrate the effectiveness of centrally coordinated programs focused on women, children, minorities, and other underserved populations in both urban and rural settings."	1. In October 1993, NIDA issued a Request for Applications for establishment of Drug Dependence Research Centers to provide a stable environment coordinated research on the efficacy of behavioral and pharmacologic treatment services. Special emphasis will be placed on the inclusion of women, children, minorities, and the underserved.

Item	Action Taken or To Be Taken
Behavioral Research	
2. The Senate in its report 103-143, page 113, stated: "The committee also encourages NIDA to continue responding to the alarming increase in the incidence of AIDS among intravenous drug users, and the Committee strongly urges NIDA to increase its behavioral research portfolio to address the association between drug use and behaviors that put these individuals at risk for HIV/AIDS."	2. A major activity is the AIDS Community-Based Intervention Study--the first multi-site cooperative agreement conducted with IDUs using targeted sampling procedures, eligibility criteria, standard intervention, and pre- and post-intervention assessments common across 21 research sites. NIDA plans to collaborate with NIAID on two multi-site studies to increase attention to drug abuse factors in research on HIV infection in women and pediatric populations. A joint announcement with CSAT in the area of linkage of drug abuse treatment and primary medical care is being prepared. A second announcement is planned to highlight HIV prevention and treatment issues, including issues unique to those who are already seropositive.
High-risk youth	
3. The Senate in its report 103-143, page 113, stated: "The committee is pleased with the coordinated research projects undertaken by NIDA and NIMH and encourages further such projects, especially systematic research efforts on early intervention aimed at preventing substance abuse and conduct disorder in high-risk youth."	3. NIDA collaborates with NIMH as well as other PHS agencies to coordinate programs, to share information, and to jointly support the costs of research in the effort to determine the etiology of high risk behaviors and to develop the means for the early identification of high risk youth. These activities have included joint and supplemental funding of research projects, multi-institute program announcements, and multi-institute scientific conferences. These efforts will continue in FY 1995.

Item	Action Taken or To Be Taken
4. The Senate in its report 103-143, page 113, stated: "The Committee urges the development of a family focused research program that will identify early risk factors for substance use and abuse among rural children and adolescents. Identification of these risk factors provides the basics for programs designed to prevent substance use problems in rural areas. The Committee requests a report from NIDA describing its response to and accomplishments from this program of rural research.	4. NIDA supports a significant program of research on drug use and abuse in rural communities. Over the past five years, NIDA has supported 17 individual studies for a total expenditure of $18.3 million. A report describing this program has been prepared for the Committee.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation	Section 301	42 Sec 241	Indefinite	$275,365,000	Indefinite	$285,135,000
National Institute on Drug Abuse..............	Section 464L	42 Sec 285o	Indefinite		Indefinite	
Medication Development....	Section 464P	42 Sec 285o-4	$95,000,000		Indefinite	
National Research Service Awards..........	Section 487(d)	42 Sec 288(d)	$400,000,000 1/	$6,460,000	Such sums as necessary 1/	$6,828,000
Total Budget Authority..				$281,825,000		$291,963,000

1/ This training authority is shared with other research training programs of the Public Health Service.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	N/A	N/A	$410,502,000	$403,806,000 2/
1994	$407,098,000	$425,201,000	425,201,000	425,201,000
1995	291,963,000 3/			

N/A - Not Applicable.

1/ Reflects enacted supplementals, rescissions, reappropriations and reductions. Prior to the FY 1993 Senate Allowance, NIDA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $3,272,000, $430,000, and $1,474,000.

3/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:										
Drug abuse and addiction.	---	$221,028	---	$231,275	---	$233,962	---	$238,632	---	$248,342
Intramural research........	127	17,685	126	18,685	137	18,638	114	18,686	108	18,678
Research management and support.............	248	22,255	292	23,871	287	24,442	287	24,507	282	24,943
Subtotal, obligations....	375	260,968	418	273,831	424	277,042	401	281,825	390	291,963
Unobligated balance lapsing.................	---	---	---	+51	---	+94	---	---	---	---
Total, budget authority....	375	260,968	418	273,882	424	277,136	401	281,825	390	291,963

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Justification

National Institute on Drug Abuse

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
424	$277,136,000	401	$281,825,000	390	$291,963,000	-11	+$10,138,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Institute on Drug Abuse. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The National Institute on Drug Abuse (NIDA) is the lead Federal agency and predominant source of funding in the United States of research on drug abuse, dependence, and addiction. Through the intramural research program at the Addiction Research Center in Baltimore, Maryland and through research grants and contracts at research institutions across the country, NIDA seeks to explore the scientific bases for the development of effective biomedical, behavioral, and psychosocial approaches to the prevention and treatment of drug abuse, and for supporting research on the relationship between drug use and AIDS, tuberculosis, and other medical problems. In addition, NIDA supports research training and career development, and science education. NIDA funds almost 90% of research on drug abuse in this country. Since relatively little drug abuse research is conducted elsewhere in the world, most of what is known about drug abuse and addiction has been derived from NIDA funded research. Four percent of the Federal budget for drug abuse control is spent on research and development, which includes NIDA research.

Drug addiction costs American society $67 billion each year in health, social, and law enforcement costs. Illicit drug use plays a considerable role in costs associated with health care services including physician visits, hospitals, emergency rooms, and other treatment facilities. Care in drug treatment centers accounts for nearly $900 million of direct health care costs. Each year, illicit drug users make more than 370,000 hospital emergency room visits, and the costs associated with short hospital stays account for approximately $1.9 billion in direct health care costs.

Estimates of the amount of money channeled out of the economy each year through the purchase of drugs vary between $25 to $110 billion. This is roughly equivalent to the net worth of the U.S. construction industry and more than double the combined profits of all Fortune 500 companies. Drug related crime is paralyzing our cities; almost one-third of those convicted of burglary committed their crimes to obtain money to purchase drugs. In FY 1992, law enforcement agencies reported nearly one million arrests for drug abuse violations. One-half of all arrestees tested positive for cocaine, and 75% of jail inmates have used drugs.

With the terrible toll in human terms on individuals and their families and the social and economic costs associated with the spread of HIV infection within and by the drug abusing population, effective drug abuse prevention and treatment are necessary now more than ever. Through research conducted and supported by NIDA we have been able, with some success, to ameliorate some of the many consequences that stem from this devastating disorder; but much still remains to be done.

NIDA-funded researchers were responsible for the discovery of opiate receptors in the brain and endogenous opiate peptides, discoveries that revolutionized the field of neuroscience. NIDA-funded researchers recently cloned several opiate receptor subtypes, an achievement that should contribute significantly to efforts to understand and treat not only heroin abuse, but also pain. More recently, NIDA scientists have made significant advances in efforts to understand and treat cocaine addiction, the most significant of which is the isolation and cloning of the dopamine transporter to which cocaine binds, and this achievement will lead to the development of more effective medications for the treatment of cocaine addiction. NIDA research has been critical to the development of new medications such as naltrexone and LAAM for the treatment of heroin abuse.

During the past decade, revolutionary brain imaging techniques, paired with quantified electrophysiology and cerebral blood flow measures, have allowed for direct visualization of the structure and activity of the brain during the administration of drugs of abuse. These technologies are providing extraordinary opportunities for insights on how drugs affect the central nervous system and how these changes correlate with human behavior and with changes during drug abuse treatment and relapse.

Drug abuse is a chronic, relapsing disorder, the treatment of which has had to surmount such inherent difficulties as heterogeneity of the patient population, polydrug use as the norm, and the lack of agreed upon criteria of treatment success. Nonetheless, high quality drug abuse treatment is available. NIDA's research in this area is paying significant dividends in terms of learning about the key factors involved in entry into drug abuse treatment; increasing recruitment, increasing retention and compliance and decreasing relapse; and better matching of drug abuse patients to treatment modality.

NIDA research has identified specific behavioral, psychosocial, and cultural factors that influence drug use, and these findings are being used to design and test a range of prevention strategies. NIDA supports a number of large-scale efforts to identify the most effective prevention strategies so that these can be implemented across the country. NIDA prevention initiatives focus on high-risk groups such as runaways, school dropouts, adolescents showing psychiatric disturbance, women and men prostitutes, unmarried pregnant women, and teenage parents.

The President's appropriation request of $291,963,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute on Drug Abuse during the last five years has been as follows:

	Amount	FTE
FY 1990	$236,932,000	360
FY 1991	260,968,000	375
FY 1992	273,882,000	418
FY 1993	277,136,000	424
FY 1994	281,825,000	401

Purpose and Method of Operation

NIDA's intramural and extramural research programs support basic, clinical, and applied research studies of drug abuse and addiction and related conditions. In addition, NIDA supports research training and career development, science and public education, and research dissemination.

Drug abuse research is a diverse area of scientific inquiry, with activities ranging from basic studies of molecular mechanisms to applied studies of drug abuse in the workplace. Taken together, this research represents the efforts of thousands of scientists working together in several disciplines: epidemiology, psychology, sociology, psychiatry, pharmacology, biochemistry, clinical medicine, and the neurosciences.

Overall Budget Policy

The FY 1995 budget request for NIDA research and direct operations is $291,963,000, an increase of $10,138,000, or 3.6% over the comparable FY 1994 level of $281,825,000. The request provides support for 388 noncompeting research project grants and 193 competing grants for a total of 581 projects, the same number as in FY 1994.

This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. For NIDA, the increase in noncompeting average cost is 4.9%, which results from the newer, more expensive cohort of FY 1993 projects replacing older, less expensive projects started in prior years. For NIDA, the total number of competing awards is made up of two components, 222 regular research project grants which increase by the biomedical inflator of 4.1% and 25 projects converting from the research demonstrations activity; and this cohort also increases by 4.1% over the average FY 1993 project cost.

The FY 1995 budget request will support 19 research centers at $25,292,000, an increase of 8.8% over the comparable FY 1994 level of $23,254,000. The increase above inflation will allow for supplements to continue the human neuroscience initiative begun in FY 1994.

The request includes $7,079,000 for research career programs, an amount sufficient to maintain the program at the FY 1994 levels. The number of career awards are estimated at 68 for FY 1995 and FY 1994 compared with 65 in FY 1993. The request includes $1,467,000 for clinical cooperative research grants. The request includes $6,393,000 for other research related grants. Included in this category are the small grants program, science education grants, minority institution support, and instrumentation grants. In FY 1995 research contracts and interagency agreements would be supported at $30,600,000, the same level as FY 1994.

In FY 1995 NRSA training programs request is $6,828,000, an increase of 5.7% over the FY 1994 level of $6,460,000. This amount will continue support for 256 full-time-training-positions, the same number as in FY 1994. A stipend increase has been requested, to begin in FY 1994, for undergraduate and predoctoral students and the first two years of postdoctoral trainees.

The request provides $18,678,000 for Intramural Research, approximately the same level as in FY 1992-1994. Research Management and Support would increase to $24,943,000. Both the Intramural and the Research Management budgets reflect a decrease of 3.0% in the administrative cost base, together with increases for mandatory items such as pay raise and inflation. The FY 1994 administrative cost estimate for NIDA will be changed to reflect a technical adjustment. The FY 1994 current estimate is $39,781,000, a decrease of $900,000 from the amount specified in the FY 1994 appropriation bill.

National Institute on Drug Abuse

Extramural Research

Authorizing Legislation - Section 301, 464L, and 464P of the Public Health Service Act. FY 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$233,962,000	$238,632,000	$248,342,000	+$9,710,000

The drug abuse and addiction activity represents the extramural research and research training programs of NIDA. Funding for Extramural Research during the last five years has been as follows:

	Amount
FY 1990	$202,029,000
FY 1991	221,028,000
FY 1992	231,324,000
FY 1993	233,962,000
FY 1994	238,632,000

Rationale for the Budget Request

With the FY 1995 extramural request these funds will provide support for the following activity: drug abuse and addiction, $248,342,000, an increase of $9,710,000 or 4.1% over the FY 1994 estimate of $238,632,000.

Neuroscience

Great advances have been made in our understanding of the biology of the brain. Expanded research in the neurosciences is leading to answers to the most central and baffling problems of addiction, such as why drug-induced euphoria occurs; what structures and systems mediate drug effects; how environmental variables and cues, learning, and memory interact in the addiction process; what biological and behavioral mechanisms are responsible for craving, abstinence, tolerance, and dependence; and why it is so difficult to break the addiction cycle. We now know that most abused drugs affect the brain by interacting with specific neurotransmitters and the receptor sites where these chemicals are active. Recent advances in molecular biology have created the opportunity to better understand the mechanisms by which cellular activity and structure affect the function of neurotransmitter receptors and other proteins in the addiction process. These technical advances provide the means for investigating individual differences in response to drug treatment and the genetic predispositions to drug abuse and addiction treatment.

Relapse is a serious problem in the treatment of drug addiction. Relapse and drug craving may be related to drug induced neuronal changes that involve alterations in receptor density, transmitter turnover, or thresholds for neuronal firing. Studies can now focus on the precise means by which specific receptors are regulated. As part of this effort, investigators will explore signal transduction pathways and factors that control regulation of genes that code for proteins involved in drug addiction, as well as processes associated with modifications of transporters, channels and other protein products important in the biological bases of drug abuse.

For example, researchers have cloned the mu, kappa, and delta opiate subtypes. The mu receptor has a pharmacologic profile that identifies it as the site involved in morphine and heroin action. Scientists have recently discovered that nitric oxide is formed by neurons, and in excess it may be responsible for the neurotoxic effects of certain drugs. The tolerance that develops to the analgesic effects of morphine is blocked by an inhibitor of nitric oxide production; but it is not blocked for opiates which involve the kappa receptor, suggesting discrete analgesic mechanisms for the different opiate receptor subtypes. Other studies by NIDA-funded researchers indicate that anandamide, an arachidonic acid derivative, may be an endogenous ligand for the cannabinoid receptor, the binding site of marijuana. Anandamide inhibits the specific binding of a radiolabeled cannabinoid probe to brain membranes, indicating that anandamide can displace marijuana from its receptor. This important finding may one day lead to a better understanding of marijuana's biological effects.

A cornerstone of NIDA's research efforts has been to better understand the relationship between brain mechanisms that underlie behaviors and how these processes are changed by drugs. NIDA-funded research using animal models has clearly demonstrated that drug addiction directly involves brain reward systems that mediate the pleasurable effects of drugs. Recognition of these systems and the advances in cellular and molecular biology come at a time when new approaches for imaging allow for direct visualization of the structure and activity of the brain in man. Paired with electrophysiology and cerebral blood flow measures, brain imaging studies may provide a means to assess cognitive function, feelings of euphoria/dysphoria, and levels of drug craving that can be related directly to underlying brain changes. For example, using positron emission tomography (PET) techniques, scientists can readily obtain images of the profound and long-lasting effects that cocaine can have in reducing blood circulation in numerous cortical areas.

Armed with these technologies, the opportunity now exists to conduct more rigorous studies of the interaction of drugs of abuse, medications, and behavioral therapies. NIDA is well positioned to bring this scientific capability--coupling neuroscience with clinical treatment--into the drug abuse clinic to help explain how individuals become addicted and to devise new therapeutic interventions. Through studies focused on the neuroscience of addiction, investigators will measure neuroanatomical, chemical and physiological parameters associated with drug use during the various stages of addictive disorders including craving, tolerance and dependence, withdrawal, and relapse. For various drugs and use patterns, studies will focus on identifying neuronal systems associated with reinforcement and brain reward, the biochemical mechanisms through which they function, and the effects of drugs upon these systems. Imaging techniques also hold the promise of being a diagnostic tool for identifying individuals who are at high-risk for drug abuse and for targeting specific treatment strategies.

NIDA and five other Federal agencies have launched the Human Brain Project, an ambitious attempt to develop a computer network of neuroscience information leading to the development of three-dimensional computerized maps and models of the structure, functions, connectivity and pharmacology of the brain at all levels from the molecular to the behavioral.

Medications Development

In FY 1990, NIDA established a medications development program to accelerate the speed with which compounds are developed as new medications for the treatment of drug abuse and dependence. In just three years (the industry average is 10 years), the program has been successful in bringing forward a medication, levo-alpha-acetylmethadol (LAAM), for the treatment of heroin addiction. A large, 26 site trial of LAAM in over 600 patients formed the basis for its approval. Utilizing electronic filing of study data and "real time" review by the FDA, LAAM was approved in just 14 working days. LAAM offers the option of every other day or thrice weekly dosing to patients, negating the need for daily clinic attendance and take-home medications except in unusual circumstances.

Non-opiate medications are also being evaluated for their utility in the medical management of opiate withdrawal and the maintenance of an opiate-free state. Recent studies indicate that clonidine and similar agents (e.g., lofexidine) appear to be effective in allowing for rapid and effective withdrawal management. A depot (injectable) formulation of naltrexone is under development to increase compliance in previously opiate dependent patients.

The development of the nicotine patch, which is widely used to aid cessation of smoking, was made possible through NIDA funded studies that demonstrated the addictive potential of nicotine and provided the basic neuroscience information necessary for patch development. Similarly, NIDA scientists have made significant advances in efforts to understand and treat cocaine addiction. Cocaine has been hypothesized to exert its characteristic euphoric effects through its binding to a dopamine transporter molecule, thus blocking the reuptake of dopamine in certain brain pathways. This blockade interferes with normal chemical neurotransporter activity, and initiates the sequence of events that ultimately cause the drug's effects. NIDA scientists have now identified an amino acid residue on the transporter protein that recognizes cocaine; but not dopamine, the endogenous transmitter. These results suggest it is possible to define different regions on the transporter that bind cocaine and dopamine. Thus, it is conceivable that a medication may be developed which interferes with cocaine binding but not the reuptake of dopamine. NIDA has developed a Cocaine Dependence Treatment Program that consists of a preclinical component to evaluate prospective compounds for clinical trials through a panel of tests (including cocaine binding and dopamine uptake) linked to a "decision tree"; and a clinical component that evaluates candidate medications in clinical trials in cocaine dependent patients. This program will be expanded in FY 1995.

Epidemiology and Prevention

NIDA supports a broad program of epidemiologic, vulnerability, and ethnographic research on the nature, patterns, extent, causes and consequences of drug abuse. Research includes studies on the incidence and prevalence as well as differential patterns of drug abuse among specific population groups; identification of risk and protective factors; identification of high risk and underserved populations; economic, demographic, and sociopsychological aspects of drug abuse; and state-of-the-art statistical and methodological approaches.

Incidence and prevalence data on high risk groups and information on vulnerability factors are needed in order to construct risk profiles for early identification of individuals at risk of initiating drug use and at risk of developing abusive patterns of use. Patterns of abuse of drugs have changed dramatically since the 1960s. Marijuana, LSD and heroin dominated the mid to late 1960s, and by the mid 1970s young drug users began the use of other drugs such as amphetamines, hallucinogens and barbiturates. As heroin use declined by the mid 1970s, the multiple drug user became the norm on the streets, in jails and in drug abuse treatment programs. Cocaine use increased significantly in the mid to late 1970s and dominated the 1980s, and there was a significant increase in social problems associated with cocaine/crack use.

Despite overall decreases in drug use by the general population in the 1980s, the NIDA-sponsored Monitoring the Future project shows an increased use of marijuana among 8th, 10th and 12th grade students. Drug use among Americans aged 35 and older, account for an increasing proportion of all users. The high purity of heroin available on the streets, coupled with fear of AIDS, is contributing to an increase in intranasal use of heroin--a route of administration that may attract new users, as well as "designer" drugs, (e.g., ecstacy) which appear to be increasingly popular.

NIDA will continue to support studies in several important areas. Though it is known that rural communities have, on average, about the same levels of drug use as urban areas, there is a dearth of epidemiologic data on patterns of use. Rural communities need special assistance gathering information about local drug problems and in developing drug prevention and treatment programs tailored to their localities. In addition, NIDA plans to expand research in examining ways to improve the validity of self-reported drug use on surveys (e.g., biological measures and improved survey methodologies). NIDA will also expand secondary analysis of data from prior drug studies, such as the National Household Survey of Drug Abuse, which has been under analyzed.

Drug prevention in this country involves multiple channels of communication beyond education in the schools and includes anti-drug media campaigns, parent education programs, community coalitions, peer group programs, and changes in health policy. In the aggregate, research has shown that these programs are creating an anti-drug use social norm that has the effect of dampening individual drug use behaviors as evidenced by lower current levels of adolescent drug use compared to 1979. However, there is a need for research to evaluate existing programs and to assess innovative prevention intervention models to reach both the general population and those at high risk for drug abuse.

Research on high-risk children has demonstrated that interventions with both children and parents can alter drug use risk factors. NIDA will expand research to better understand vulnerability to drug addiction, leading to the design and testing of prevention interventions especially targeted to youth at risk of multiple problem behaviors. These studies are significant because they address risk factors that occur before drug use initiation and because they target risk factors implicated in a range of disorders, including drug abuse as well as anti-social behavior, delinquency, and adult criminality.

Violence related to obtaining funds to purchase drugs and violence associated with drug distribution activities appear to be on the increase. NIDA supports studies of the interactive roles of psychological, cultural, community, and other larger societal factors that expose individuals to or protect them from violence associated with illicit drug use.

Health Services Research

NIDA supports a significant portfolio of research on the organization, financing, and management of health services and their impact on the quality, cost, and outcomes of care both within established service delivery settings and at a system-wide level. In addition, research in this area seeks to understand the relationship between drug abuse treatment and the delivery of services within other organized systems, (e.g., social welfare, criminal justice, mental health, primary health care systems). With the renewed interest in health care reform, studies on the factors that influence the availability, accessibility, and utilization of health services, and the efficiency and effectiveness of these services have taken on special urgency.

Treatment retention and relapse remain problematic for many segments of drug abusers. Progress has been made in key areas of treatment services research, such as the differential effectiveness of treatment programs, the improvement of treatment, client assessment, and matching services to client needs. Recent findings demonstrate the critical importance of services in drug abuse treatment programs. In a study of methadone patients stabilized on 60 mg/day of methadone, three levels of treatment intensity were compared: 1) minimal services, with counseling provided on an emergency basis, 2) standard counseling, and 3) enhanced services, with counseling and other services such as medical/psychiatric, employment counseling, and family therapy. Nearly 70% of the minimal-service clients had to be protectively transferred to more intensive treatment because of unremitting opiate/cocaine use or medical/psychiatric emergencies, while only 41% of clients in "standard" treatment, and 19% in enhanced treatment continued to experience these problems.

Length of time in drug abuse treatment is well-correlated with favorable outcomes. In a study of public treatment facilities, clients referred by the criminal justice system were retained longer than others, and drug use and criminal activity decreased substantially during treatment. Cost effectiveness of treatment, as measured by crime-related costs, was related to length of stay in treatment. Drug associated costs of crime in the year after treatment were substantially lower. Studies to investigate the drug-crime connection are also an integral part or our research program, and we have worked with agencies within the criminal justice system to identify interventions that are most successful in engaging and retaining drug-using offenders into drug abuse treatment.

Access to appropriate treatment is often problematic for reasons that have to do with the organization and distribution of treatment resources, cost, financing, and utilization. High risk populations such as adolescents with multiple problems, the physically disabled, pregnant women, homeless, and mentally ill drug abusers present very different service needs and access issues than other treatment groups. Linkages of drug abuse treatment with primary health care will be further examined. NIDA will develop and test more effective strategies such as street outreach and criminal justice linkages, new strategies to recruit clients into treatment, and service delivery strategies for treatment-resistant/avoidant clients such as mobile or street-based treatment.

NIDA has taken a number of steps to strengthen its health services research program. Last year, NIDA issued a Request for Applications to solicit new studies on health services issues as they relate to drug abuse treatment. NIDA is encouraging health services research that addresses not only drug abuse treatment but also prevention of HIV transmission and other medical consequences associated with drug abuse. A Treatment Services Research Branch was established. NIDA is also preparing a 5-year plan for drug abuse health services research. New research will examine such issues as the demand for and delivery of treatment in a variety of settings, its cost, and effectiveness the effects of financing, reimbursement, and regulatory strategies on access, outcomes and quality of care; entry, compliance, and retention for patients in treatment; and effectiveness of alternative organizational and manpower configurations on treatment.

Behavioral Therapies

Research supported by NIDA holds promise for improving the quality of life for affected individuals and their families. We have learned how to improve recruitment into treatment, to better match clients to treatment modality, and to increase retention and decrease relapse rates. And we have learned the value of more intensive and comprehensive treatment in terms of such positive outcome measures as abstinence, reduced drug use, decreased crime, and increased employment and productivity.

Behavioral therapies, including a range of psychosocial interventions, are the most frequently administered treatments for drug addiction, and they are the only available treatment for many drugs of abuse. Behavioral strategies focus on factors judged to reinforce or condition the problematic drug behavior such as low achievement in employment/education; cognitive and perceptual factors such as attitudes, values, emotions; psychological symptoms; and behavior in social roles such as in the family and peer groups. Behavioral approaches include interventions such as contingency management in which the frequency of individual behavior is modified through its consequences, and the more comprehensive community reinforcement approach, in which reinforcers within the broader community are also used to modify behaviors. Psychosocial treatment approaches also include psychotherapy, drug abuse counseling, and vocational rehabilitation.

Effective treatment of drug addiction requires a comprehensive approach to dealing with a patient's multiple problems. Providing an optimal combination of services for each client is critical to successful treatment outcome. To enhance the ability to match patients to treatments more needs to be learned about the interpersonal and environmental factors which influence drug treatment. Treatment of coexisting psychiatric problems has been shown to improve treatment outcomes and reduce relapse. Matching patients to the appropriate treatments results in increased treatment engagement, retention, and compliance. NIDA research is focused on how greater levels of effectiveness can be achieved through more specific treatment applications and to find better methods of providing patients optimum levels of care. Replication of treatment results is made difficult by the fact that client populations differ within and across treatment types both by drug of abuse and by level of impairment.

Systematic research on behavioral therapies for drug abusers is in its early stages. Although many forms of behavioral therapy exist, most were not developed or tested specifically for drug abusers. For drug abuse treatment to succeed, it is essential that all phases of behavioral treatment research receive sufficient emphasis and support. In recognition of the importance of psychosocial and behavioral treatment research, NIDA has developed plans for a multi-phase initiative in this area. The Behavioral Therapies Development Program will complement and expand work currently underway.

The initiative will include four phases. Phase I involves identifying promising research findings relevant to drug abuse treatment, generating and formulating new psychobehavioral therapies, operationally defining the therapies in manuals, and pilot testing and modifying the therapies. Support for this phase began in FY 1993 and continues under the budget request. Phase II continues NIDA's program of small-scale efficacy testing of promising therapies and the replication, at other sites, of efficacy studies with positive results. Phase III will consist of large-scale testing of therapies shown to be efficacious in more than one controlled clinical trial. This will involve multi-site studies of efficacious therapies to determine their effectiveness in community-based treatment programs. In Phase IV, results of Phase II and III studies will be evaluated by panels of experts, and where substantial evidence for effectiveness is demonstrated, the therapy will be packaged in a way that practitioners can apply it most effectively.

Parental Drug Abuse

Parental substance abuse has the potential to adversely affect the developing child. NIDA research seeks to understand the effect of prenatal drug exposure, to find effective means of treating drug abuse during pregnancy and to find treatments to mitigate adverse consequences to drug-exposed children.

Drug abuse during pregnancy may cause a number of adverse consequences to the offspring. The duration and onset of effects may vary. For instance, effects seen during the child's first month may disappear by the end of the first year. On the other hand, if negative effects do not immediately appear, this does not mean that drug effects will not exert a profound influence at some later date.

Animal studies indicate that there are biological and behavioral effects of prenatal and early postnatal exposure to drugs of abuse. Clinical research indicates that in utero exposure to cocaine is associated with lower gestational age, low birth weight, smaller head circumference, small body size for gestational age, and increased length of stay in the hospital. Infants exposed to substance abuse in utero often exhibit irritability and/or lethargy, and thus may have difficulty in responding to maternal interactions. Animal research also indicates that the cardiovascular system during pregnancy may be more sensitive to adverse effects of cocaine due to pregnancy related changes in progesterone levels. The course and timing of labor may also be affected by maternal cocaine use. More research is needed to fully understand these phenomena.

Parental drug use can also put infants at increased risk of negative familial and environmental effects, including and abuse neglect. By nine years of age, such factors dominate as the pervasive influences in dysfunctional development of children in drug abusing families. As a group, drug-using mothers are found to be less sensitive to their children's cues, less positive toward their children, and less encouraging of learning. Drug use by the father, too has an impact on the family and child; and this relationship needs to be more fully explored.

Research is needed to improve the assessment and treatment of children exposed to drugs, including longitudinal studies to follow the behavioral and physiological development of drug-exposed children to determine whether deficits result from exposure, and studies on the extent to which children of drug abusing parents may be more likely to have problems with drug abuse or other behaviors by virtue of genetic, familial, or environmental factors. Research will assess the full range of brain development and maturation, including possible relationships between early or chronic drug use and brain function in later life and the onset of subsequent neurological disorders. Particular emphases will be placed upon studies that assess prenatal and perinatal effects of in utero drug exposure through a variety of cognitive function and behavioral tests.

An area of increasing urgency is the design and testing of medications effective in the treatment of pregnant women. New and expanded efforts are needed for the development of medications that do not cross the placenta or are not active in the fetus, so that drug dependent and addicted pregnant women can receive pharmacologic treatment without major influence on the developing fetus.

Research Training and Career Development

Research training and career development efforts are intimately linked to the availability of an adequate supply of well-trained biomedical and behavioral researchers and to the long-term success of addiction research. NIDA must continue to focus on research training and recruitment activities in order to ensure that sufficient numbers of trained and qualified research scientists are investigating the issues and problems of drug abuse. To address these problems, increased support is provided for both traditional and innovative training mechanisms to increase the pool of students interested in drug abuse and addiction-related research, especially those working in clinical research, medications development and epidemiology.

The ability to transfer basic research into clinical applications relies heavily on clinicians who are trained in the drug abuse research field. Unfortunately, research efforts have been hampered by the relatively small numbers of clinically trained persons who choose drug abuse research as a career. To fill the demand for expertise in the complex area of medications development, NIDA has established an initiative that involves trainees with both the private industry and the Food and Drug Administration. This linkage will provide individuals highly specific, intensive, and comprehensive research and regulatory experiences that will maximize their effectiveness and productivity following the training period.

Epidemiology is another chronic shortage category, and training opportunities in descriptive and analytical epidemiology and methodology development and improvement will be expanded for fellows pursuing research in the epidemiology of illicit drugs and nonmedical use of licit drugs.

A culturally diverse research workforce provides a unique and valuable perspective in addressing abuse in minority populations. NIDA will continue its support of mechanisms to promote the recruitment and retention of women and minorities to drug abuse research as well as short term training opportunities for the purpose of recruiting individuals into addiction research careers.

National Institute on Drug Abuse

Intramural Research Program

Authorizing Legislation - Section 301, 464L, and 464P of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
137	$18,687,000	114	$18,686,000	108	$18,678,000	-6	-$8,000

The NIDA intramural research program at the Addiction Research Center (ARC) in Baltimore, Maryland is the largest single drug abuse research program in the world. The ARC conducts interdisciplinary research on the nature of the addiction process; the causes, hazards, prevention and treatment of drug abuse; and the abuse liability of drugs. Over 100 research projects in the basic neurosciences, clinical pharmacology, and behavioral sciences are conducted yearly. Having an intramural team of scientists allows the Institute to respond quickly to changing patterns of drug use, and the diversity of expertise at the ARC provides an exceptional environment in which to conduct drug abuse research.

Funding for the Intramural Program during the last five years has been as follows:

	Amount	FTEs
FY 1990	$16,583,000	112
FY 1991	17,685,000	127
FY 1992	18,687,000	126
FY 1993	18,687,000	137
FY 1994	18,686,000	114

Rationale for the Budget Request

The FY 1995 budget request for the Intramural Program is $18,678,000, as compared to $18,686,000 provided in FY 1994. In FY 1995, total staffing will be 108, compared to 114 in FY 1994.

Genetics of Drug Self-Administration

Recent studies have demonstrated that genotype significantly affects an individual's vulnerability to the acute and reinforcing effects of abused drugs. Current initiatives are aimed at developing an intravenous self-administration model in the species ideally suited for genomic research, the mouse. Together with a previously established genetic data based, this model will enhance our ability to use an established repertoire of unique genetic tools as well as newly developed transgenic mice with specific alterations in receptors known to influence the behavioral effects of abused drugs.

Evaluation of High affinity Dopamine Uptake Inhibitors as Cocaine Substitutes

The ability of cocaine to increase brain dopamine by blocking its uptake into nerves is thought to produce its addictive and euphoric effects. One strategy for treating cocaine addiction is to develop a medication which occupies the same molecular receptor as cocaine, but which does not increase dopamine to the same extent. Such a drug would be expected to block the effects of cocaine and to decrease cocaine-craving. To be useful as a treatment for cocaine, such a drug must not possess the euphoric effects of cocaine. Previous studies showed that the high affinity dopamine uptake inhibitor GBR 12909 partially blocked the ability of cocaine to increase brain dopamine in rats. This agent, which does not produce euphoric effects when administered to humans, completely suppresses cocaine seeking behavior in rhesus monkeys. ARC scientists will build on these initial successes by synthesizing more potent and effective agents. We also hope to conduct pilot studies in humans with selected agents.

Novel Medications for the Treatment of Opioid Addiction

Recent studies have implicated opioid kappa receptors in the development and maintenance of addiction to opioid drugs. Kappa receptors also appear to modulate the effects of cocaine thought to be relevant to its addictive actions in humans. Previous studies have identified six subtypes of the opioid kappa receptor. ARC scientists will synthesize selective kappa receptor agonist and antagonists. These agents will provide the needed tools to determine the role of kappa opioid receptors in health and pathological states such as addiction.

Structure and Function of the Opioid Receptor/Endorphin System

The central nervous system opioid receptors and their endogenous ligands, termed the endorphins, comprise a complex neuronal system which modulates pain, mood, thought processes and numerous other bodily functions. ARC scientists have identified several subtypes of the opioid receptors: six kappa receptors, four delta receptors and two mu receptors. These studies continue to produce drugs of defined selectivity which provide the needed tools to determine the role of opioid receptor subtypes in health and pathological statues such as addiction. Recent work has focused on the development of highly selective and systemically active non-peptide delta receptor agonist and studies designed to relate the cloned opioid receptors to the previously pharmacologically defined receptor subtypes.

Role of Dopamine in Human Cocaine Reward

The reinforcing ("addicting") effects of cocaine for animals involve certain receptors in the dopaminergic reward system. These findings have led to considerable activity by Federal and industrial laboratories to develop medications to treat cocaine addiction by modulation of the dopaminergic system. Unfortunately, there are no human data that indicate which of the potential dopaminergic target receptor sites mediate the rewarding effects in humans. ARC scientists will investigate medications known to act at each of the dopamine receptor sites to determine which is responsible for the rewarding affects of cocaine in humans.

Identification of Changes in Gene Expression Produced by Drugs

Recent studies at the ARC, including the cloning of the primary sites of action of cocaine and morphine, have advanced our understanding of the molecular mechanisms of acute drug action. Newly developed molecular neurobiological techniques can identify each of the genes whose expression changes in short and long-term responses to abused drugs. ARC scientists are working to identify genes whose expression changes following acute and chronic drug use and attempt to identify the role that these genes altered expression plays in the development of tolerance and dependence.

Genetic Factors in Drug Abuse

Classical genetic studies of drug abusers have indicated that a substantial component of vulnerability to abused drugs is genetic. This genetic influence is likely to be contributed by several genes. Identification of genes which increase vulnerability for drug abuse will be undertaken by identifying populations that maximize the genetic component to risk (concordant twin pairs), establishment of immortalized cell line DNA banks from drug abusers and matched non-abusers, studying candidate genes involved in biochemical mechanisms of drug action, and studying anonymous genetic markers closely spaced across human chromosomes. These studies will allow identification of genes associated with drug abuse vulnerability and provide the possibility for targeting intervention strategies in individuals most at risk.

National Institute on Drug Abuse

Research Management and Support

Authorizing Legislation - Section 301, 464L, and 464P of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
287	$24,487,000	287	$24,507,000	282	$24,943,000	-5	+$436,000

This activity provides the resources for the scientific leadership and overall management and scientific direction of the Institute. Funding for Research Management and Support during the last five years has been as follows:

	Amount	FTEs
FY 1990	$18,320,000	248
FY 1991	22,255,000	248
FY 1992	23,871,000	292
FY 1993	24,487,000	287
FY 1994	24,507,000	287

Rationale for the Budget Request

The FY 1995 budget request for Research Management and Support is $24,943,000, an increase of $436,000, or 1.8% over the $24,507,000 provided in FY 1994. In FY 1995, total staffing will be reduced to 282, a reduction of 5 from FY 1994.

The Office of the Director plans and directs all NIDA activities, and coordinates programs in special populations research. The Office of Planning and Resource Management provides financial, personnel, information resource management, administrative services, grant and contract administration, and oversight of Equal Employment Opportunity programs. The Office of Extramural Project Review coordinates the scientific review of grant and contract applications. The Office of Science Policy, Education, and Legislation directs the science planning process, and performs technology transfer functions. The Office is the principal liaison with drug abuse professionals, state and local governments, the press and the general public.

Four program divisions--Basic Research, Clinical Research, Epidemiology and Prevention Research, and Medications Development--are responsible for planning and administration of the Institute's research activities. In addition, the Division of Epidemiology and Prevention Research works with local, state, federal, and international government agencies in developing drug abuse surveillance capability through the establishment of epidemiology networks.

NATIONAL INSTITUTES OF HEALTH

National Institute on Drug Abuse

Detail on Full-Time Equivalent Employment

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director..........	21	21	21
Office of Planning & Resource Management...........	66	66	65
Office of Extramural Program Review................	35	35	34
Office on AIDS..................	2	2	2
Division of Basic Research......	24	24	24
Division of Clinical Research...	40	40	40
Division of Epidemiology & Prevention....................	26	26	25
Office of Science Policy, Education & Legislation.......	37	37	36
Medications Development Division	36	36	35
Addiction Research Center.......	137	114	108
Total, NIDA.................	424	401	390

Average GS/GM Grade	
1990............	10.5
1991............	10.6
1992............	10.7
1993............	10.9
1994............	10.9
1995............	10.7

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

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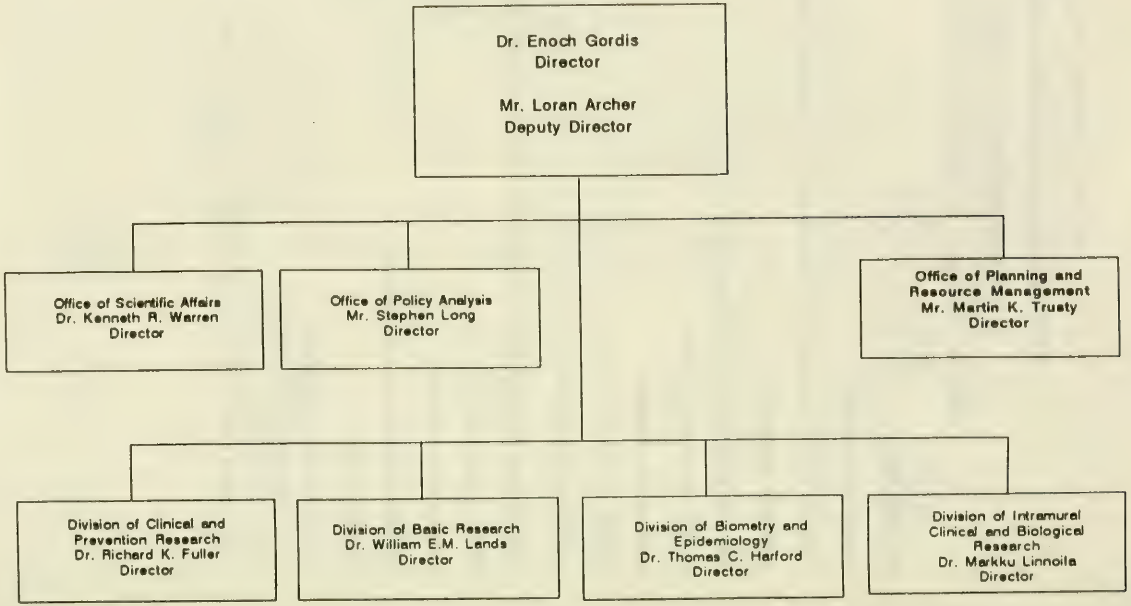
NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

For carrying out section 301 and title IV of the Public Health Service Act with respect to alcohol abuse, and alcoholism, [$185,617,000] *$182,498,000 of which $2,015,000 shall not become available for obligation until September 19, 1995.* *(Department of Labor, Health and Human Services Appropriation Act, 1994.)*

National Institute on Alcohol Abuse and Alcoholism

Language Analysis

Language Provision	Explanation
"...of which $2,015,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation....................	178,711,000	185,617,000	182,498,000
Section 511 .8% Reduction.........	-1,430,000	---	---
Section 513 Consultant services		---	---
reduction......................	-61,000	---	---
Section 216 S & E Reduction.......	-601,000	---	---
Subtotal, adjusted appropriation	176,619,000	185,617,000	182,498,000
Real transfer to other NIH accounts for tuberculosis research......................	-173,000	---	---
Comparative transfer to the Office of AIDS Research, NIH for HIV activities............	-6,823,000	-9,457,000	---
Subtotal, adjusted budget authority.....................	169,623,000	176,160,000	182,498,000
Unobligated balance, lapsing......	-273,000	---	---
Total obligations.............	169,350,000	176,160,000	182,498,000

1/ Excludes the following amounts for reimburseable activities carried out under this account: FY 1993 - $2,707,000; FY 1994 - $2,064,000; FY 1995 - $1,766,000.

Note: Excludes $3,333 for royalties received in FY 1993.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects						
Noncompeting	302	$72,272,000	279	$69,280,000	291	$70,454,000
Administrative supplementals	(7)	206,000	(19)	821,000	(19)	855,000
Competing:						
Renewal	39	9,459,000	43	10,320,000	45	10,800,000
New	60	9,731,000	83	15,675,000	90	18,129,000
Supplemental	1	411,000	1	205,000	1	207,000
Subtotal, competing	100	19,601,000	127	26,200,000	136	29,136,000
Subtotal, research projects	402	92,079,000	406	96,301,000	427	100,445,000
Research Ctrs:						
Specialized/comprehensive	13	16,737,000	13	17,344,000	13	18,473,000
Other Research:						
Research career program	39	3,368,000	47	4,224,000	47	4,372,000
Cooperative clinical research	12	10,185,000	12	8,400,000	12	8,635,000
Minority biomedical research support	--	206,000	--	300,000	--	312,000
Other research related	41	3,417,000	48	3,330,000	48	3,423,000
Subtotal, other research	92	17,176,000	107	16,254,000	107	16,742,000
Total, research grants	507	125,992,000	526	129,899,000	547	135,660,000

Training:						
Individual awards:						
Noncompeting	8	175,000	14	290,000	26	651,000
Competing	11	216,000	20	466,000	8	131,000
Subtotal, individual	19	391,000	34	756,000	34	782,000
Institutional awards:						
Noncompeting	120	3,048,000	114	3,347,000	100	3,017,000
Competing	10	175,000	30	934,000	44	1,414,000
Subtotal, institutional	130	3,223,000	144	4,281,000	144	4,431,000
Total, training	149	3,614,000	178	5,037,000	178	5,213,000
Research and development contracts	13	7,057,000	29	8,091,000	29	8,359,000
	FTEs		FTEs		FTEs	
Intramural research	112	19,991,000	113	20,203,000	109	20,224,000
Research management and support	142	12,969,000	131	12,930,000	128	13,042,000
Total	254	169,623,000	244	176,160,000	237	182,498,000
Clinical trials		(17,550,000)		(18,400,000)		(19,100,000)

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institute on Alcohol Abuse and Alcoholism

Summary of Changes

1994 Estimated budget authority	$176,160,000
1995 Estimated budget authority	182,498,000
Net change	+6,338,000

	1994 Current Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural Research				
a. Within grade increases		$7,442,000		+$98,000
b. One day less pay		7,442,000		-29,000
c. Annualization of January, 1994 locality pay raise		7,442,000		+56,000
d. January, 1995 pay increases		7,442,000		+91,000
e. Unemployment compensation, Federal employees compensation fund increase		7,442,000		+5,000
f. Payment for centrally furnished services		6,512,000		+268,000
g. Service and Supply Fund increase		1,242,000		+113,000
h. Federal telecommunications system increase		244,000		+1,000
i. Increased cost of supplies materials, and other expenses		4,763,000		+167,000
Subtotal				+770,000
2. Research Management and Support				
a. Within grade increases		8,886,000		+117,000
b. One day less pay		8,886,000		-34,000
c. Annualization of January, 1994 locality pay raise		8,886,000		+92,000
d. January, 1995 pay increases		8,886,000		+109,000
e. Unemployment compensation, Federal employees compensation fund increase		8,886,000		+4,000
f. Payment for centrally furnished services		297,000		+12,000
g. Service and Supply Fund increase		669,000		+79,000
h. Increased cost of DHHS Working Capital Fund		189,000		+1,000
i. Federal telecommunications system increase		250,000		+2,000

Summary of Changes-continued

	1994 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
j. Increased cost of supplies materials, and other expenses		2,639,000		+94,000
Subtotal				+476,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a: Noncompeting	279	$70,101,000	+12	+$1,208,000
b: Competing	127	26,200,000	+9	+2,936,000
Total	406	96,301,000	+21	+4,144,000
2. Research Centers		17,344,000		+1,129,000
3. Other research		16,254,000		+488,000
4. Research training awards		5,037,000		+176,000
5. Research and Development Contracts		8,091,000		+268,000
	FTEs		FTEs	
6. Intramural Research	113	20,203,000	-4	-749,000
7. Research Management and Support	131	12,930,000	-3	-364,000
Subtotal				+5,092,000
Total changes				+6,338,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment	244	237	-7
Full-time equivalent of overtime and holiday hours	1	1	---
Average ES salary	$107,800	$108,878	+$1,078
Average GM/GS grade	10.8	10.8	---
Average GM/GS salary	$46,133	$46,825	+$457
Average salary, grades est. by act of July 1, 1944 (42 USC 207)	49,765	50,511	+$493
Average salary of ungraded positions	20,849	21,162	+$206
Personnel compensation:			
Full-time permanent	$9,830,000	$9,832,000	+$2,000
Other than full-time permanent	2,069,000	2,105,000	+36,000
Other personnel compensation	398,000	378,000	-20,000
Special personnel services	1,176,000	1,095,000	-81,000
Total personnel compensation	13,473,000	13,410,000	-63,000
Personnel benefits	2,846,000	2,813,000	-33,000
Benefits for former personnel	9,000	9,000	---
Travel and transportation of persons	331,000	350,000	+19,000
Transportation of things	81,000	85,000	+4,000

	1994 Appropriation	1995 Estimate	Increase or Decreasc
Rent, communications and utilities..........................	$2,201,000	$2,233,000	+$32,000
Printing and reproduction...........	312,000	286,000	-26,000
Consulting services.................	251,000	246,000	-5,000
Other Services......................	1,433,000	1,525,000	+92,000
Purchases from Govt. Accts..........	10,719,000	10,653,000	-66,000
R&D Contracts.......................	6,041,000	6,309,000	+268,000
Supplies and materials..............	1,781,000	1,917,000	+136,000
Equipment...........................	1,746,000	1,789,000	+43,000
Grants, subsidies and contributions.....................	134,936,000	140,873,000	+5,937,000
Total, budget authority.........	176,160,000	182,498,000	+6,338,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NIAAA

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	9,830	9,830	9,830	0
11.3	Other than full-time permanent	2,069	2,069	2,106	37
11.5	Other personnel compensation	398	398	378	(20)
11.8	Special personnel services payments	1,176	1,176	1,096	(80)
11.9	Subtotal, personnel compensation	13,473	13,473	13,410	(63)
12.1	Civilian personnel benefits	2,846	2,846	2,813	(33)
13.0	Benefits for former personnel	9	9	9	0
	Subtotal Pay Costs	16,328	16,328	16,232	(96)
21.0	Travel and transportation of persons	331	331	350	19
22.0	Transportation of things	81	81	85	4
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	2,201	2,201	2,233	32
24.0	Printing and reproduction	312	312	286	(26)
25.0	Other Services	10,353	10,353	10,374	21
26.0	Supplies and materials	1,781	1,781	1,917	136
	Subtotal non-pay costs	15,059	15,059	15,245	186
	Total Administrative Costs	31,387	31,387	31,477	90

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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National Institute on Alcohol Abuse and Alcoholism

Significant Item in Senate Appropriations Committee Report

Item	Action Taken or To Be Taken
Rural Areas	
The Senate in its report 103-43, page 111, states "*Rural areas* -- ... The Committee has provided sufficient funds for NIAAA to establish a family-focused research program that will identify early precursors of alcohol problems during childhood and adolescence in rural areas. Such research will identify early risk factors that can be targeted in the development of effective prevention programs designed to prevent the onset of alcohol abuse. Funding for this research will come from the increase allocated to NIAAA. The Committee requests a written report describing NIAAA's response to and accomplishments from this program of rural research."	NIAAA will increase its support in FY 1994 for research on alcohol problems in rural areas.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amt. Authorized	1994 Appropriation	1995 Amt. Authorized	1995 Budget Request
Research and Investigation .	Section 301	42§241	Indefinite	$171,123,000	Indefinite	$177,285,000
National Institute on Alcohol Abuse and Alcoholism.	Section 464H	42§285n	Such Sums as Necessary		Such Sums as Necessary	
National Research Service Awards	Section 487	42§288	$400,000,000	5,037,000	Such Sums as Necessary	5,213,000
Total Budget Authority . .				176,160,000		182,498,000

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	n/a	n/a	$180,169,000	$176,619,000 2/
1994	$173,615,000	$185,617,000	185,617,000	185,617,000
1995	182,498,000 3/			

n/a = Not applicable.

1/ Reflects enacted supplementals, rescissions, and reappropriations. Prior to the FY 1993 Senate Allowance, NIAAA was a component of the ADAMHA appropriation.

2/ Excludes enacted administrative reductions of $1,430,000, $61,000, and $601,000.

3/ The 1995 Request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research												
Alcohol biomedical and behavioral research........	--	$121,823	--	$133,486	--	$136,440	--	$143,027	--	$149,232	--	+$6,205
Intramural research.	98	17,193	107	17,941	112	19,991	113	20,203	109	20,224	-4	+21
Research management and support......	141	11,129	141	12,093	142	12,919	131	12,930	128	13,042	-3	+112
Subtotal, obligations.....	239	150,145	248	163,520	254	169,350	244	176,160	237	182,498	-7	+6,338
Unobligated balance, lapsing.........	--	107	--	267	--	273	--	---	--	---	--	---
Total budget authority......	239	150,252	248	163,787	254	169,623	244	176,160	237	182,498	-7	+6,338

Justification

National Institute on Alcohol Abuse and Alcoholism

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
254	$169,623,000	244	$176,160,000	237	$182,498,000	-7	+$6,338,000

General Statement

This document provides justification for Non-AIDS activities of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled, "Office of AIDS Research (OAR)".

The mission of the NIAAA is to focus the Federal government's endeavors to develop knowledge and promote strategies needed to prevent and reduce the health, social, and economic consequences of alcohol abuse and alcoholism in the United States. Today NIAAA provides national leadership to the alcohol research community and is the source of financial support for approximately 90 percent of all alcohol research in this country. NIAAA's research program encompasses a wide range of biomedical and behavioral science, such as neuroscience, genetics, medical consequences, medications development, prevention, and treatment.

As the Federal entity responsible for conducting biomedical and behavioral research on the causes, consequences, treatment, and prevention of alcohol abuse and alcoholism, NIAAA maintains a diverse research portfolio. From the molecular workings of genes and cell membranes, to intricate biochemical pathways and neural circuits, to the behavioral responses caused by alcohol ingestion; from understanding why some people drink in spite of alcohol-related problems, to fathoming how best to treat alcohol abuse, NIAAA-sponsored investigators and intramural scientists are on the leading edge of alcohol research. In order to respond to urgent research needs in the areas of Women's Health, Youth, Health Services Research, Medications Development, Prevention, and Minority Health, the Institute is designating these as areas of high priority for alcohol research in 1995.

The President's appropriation request of $182,498,000 for this account represents current law requirements. No proposed law amounts are included.

Funding for the NIAAA during the past five years has been as follows:

	Amount	FTE
FY 1990	141,243,000	240
FY 1991	150,252,000	239
FY 1992	163,787,000	248
FY 1993	169,623,000	254
FY 1994	176,160,000	244

Purpose and Method of Operation

The Division of Basic Research, the Division of Clinical and Prevention Research, and the Division of Biometry and Epidemiology are extramural research entities that support a wide range of research efforts in their respective functional areas through research grants, contracts, cooperative agreements, National Research Service Award fellowships, and training grants. The Division of Biometry and Epidemiology is also involved in data collection and analysis on distribution and determinants of alcohol abuse and alcoholism through studies and surveys.

The Division of Intramural Clinical and Biological Research includes laboratories engaged in metabolic, preclinical, and clinical research.

The Institute's staff offices provide policy analyses, peer review, and business management of grant applications and contract proposals and awards, as well as personnel, planning, management analysis, administrative, financial management activities in support of Institute programs. The Office of the Director provides overall management and direction, assesses program operations and effectiveness, and establishes the Institute's goals, objectives, and priorities.

In both its intramural and extramural activities, the Institute conducts and supports research aimed at determining the causes of alcoholism, discovering how alcohol damages the organs of the body, and developing prevention and treatment strategies for application in the Nation's health care system; serves as a national resource for the collection, analysis, and dissemination of scientific findings and improved methods of prevention of alcohol-related problems and treatment services; supports training and development of scientists for participation in alcohol research programs and activities; conducts policy studies that have broad implications for alcohol prevention, treatment, and rehabilitation activities; and conducts epidemiological studies as well as national and community surveys to assess the risks for and problems among various population groups.

Overall Budget Policy

The FY 1995 request for NIAAA is $182,498,000, an increase of $6,338,000 or 3.4 percent over the FY 1994 appropriation of $176,160,000. A program increase of $663,000 is also included in the FY 1995 request for breast cancer research.

The FY 1995 request would support 427 total research project grants at $100,445,000, an increase of 21 awards and $4,144,000 over the FY 1994 appropriation. Within this total, NIAAA would support 291 noncompeting research project grants at $70,454,000, and 136 competing grants at $29,136,000. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment. Average costs of competing research project grants would receive an increase equal to the Biomedical Research Price Deflator Index (BRPDI) of 4.1 percent.

A total of 13 research centers would be supported in the FY 1995 request at $18,473,000, an increase of 6 percent over the 1994 appropriation.

A 3 percent increase over the 1994 appropriation would be provided for other research grants. This includes 47 research careers at $4,372,000; $8,635,000 for the Cooperative Agreement on the Genetics of Alcoholism and for Project MATCH; $312,000 for Minority Biomedical Research Support; and $3,423,000 for 48 awards comprised of small grants, instrumentation awards, and conference and scientific evaluation grants.

The FY 1995 request would support 178 full-time training positions at $5,213,000, the same number of training positions as in the FY 1994 appropriation and a funding increase of 3.5 percent.

Research and development contracts would be supported at $8,359,000, an increase of 3.3 percent as compared to the 1994 appropriation.

The FY 1995 request includes $20,224,000 for intramural research and $13,042,000 for research management and support, approximately the same levels as the FY 1994 appropriation.

National Institute on Alcohol Abuse and Alcoholism

Extramural Research

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part C Sections 464H and 487. 1994 Authorization: Such sums as necessary.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$136,663,000	$143,027,000	$149,232,000	+$6,205,000

To fulfill its research mission, NIAAA places its greatest emphasis on extramural studies conducted by scientists in universities, colleges, and other institutions throughout the country to build a solid base of biomedical and behavioral knowledge for improved prevention and treatment of alcohol-related problems. This extramural activity supports studies in such areas as health services, genetics, Fetal Alcohol Syndrome (FAS), alcohol-related medical disorders, and medications development; studies that are designed to investigate alcohol treatment and prevention methods and strategies; and epidemiological research aimed at understanding the etiology of alcohol abuse.

Funding for this activity during the last 5 years has been as follows:

	Amount
FY 1990	$114,167,000
FY 1991	121,823,000
FY 1992	133,605,000
FY 1993	136,663,000
FY 1994	143,027,000

Rationale for the Budget Request

The FY 1995 request for extramural research, which consists of the activity, alcohol biomedical and behavioral research, is $149,232,000, an increase of $6,205,000 or 4.3 percent over the FY 1994 appropriation of $143,027,000.

WOMEN

Fewer women than men drink and, on the whole, women who drink consume less alcohol and have fewer alcohol-related problems than men. Yet, among the heaviest drinkers, women equal or surpass men in the number of problems that result from their drinking. The interval between onset of drinking-related problems and entry into treatment appears to be shorter for women. Women are known to be more susceptible to alcohol-induced liver damage than are men--developing severe liver disease, especially alcoholic hepatitis and cirrhosis, with shorter durations of alcohol use and lower levels of consumption. There is mounting evidence that women who abuse alcohol also have a greater risk than men of developing cardiovascular disease, hemorrhagic stroke, and reproductive and endocrine anomalies. Institute-sponsored scientists will be expanding current research efforts directed at understanding alcohol's role in the genesis or exacerbation of these diseases, as well as investigating the mechanisms of this enhanced susceptibility.

NIAAA researchers are currently examining the link between alcohol consumption and breast cancer; this is a major initiative for 1995. Some epidemiologic studies have associated chronic alcohol consumption with an increase of about 10 percent in risk of breast cancer, especially for postmenopausal women; the risk appears to increase as the quantity and duration of alcohol consumption increases. However, other studies have found no evidence of such a link, suggesting that other factors, such as nutritional deficiency and genetic susceptibility, may be responsible for the increased risk.

NIAAA is also supporting the largest and most in-depth longitudinal study of women's drinking ever conducted in the U.S. Data from this study will provide information on the antecedents, dynamics, and consequences of women's drinking. An important component of the study is to determine whether alcohol-related violence differs by gender and if women's drinking or alcohol-associated aggressive behavior may trigger their victimization.

YOUTH

The impact of alcohol abuse and alcoholism on children is profound. There are the direct and lasting effects on the growing fetus, leading to fetal alcohol syndrome, FAS. There is limited knowledge about adolescent abuse of alcohol and its effects on normal hormonal stimulation of physical and sexual development, as well as its effects on the long-term health of many organ systems and psychological development. In addition to physical effects, the impact on children during critical periods of growth and development when experiencing a dysfunctional environment secondary to alcohol abuse or alcoholism in the family is most damaging.

FAS is the severest alcohol-induced birth defect. The cellular and molecular mechanisms contributing to FAS are being investigated. For instance, retinoic acid, a form of vitamin A, is crucial to proper fetal development. Since alcohol may inhibit its synthesis, reduced levels of this vitamin in the embryo during critical periods of development may be one possible cause of abnormal fetal development. Another promising area in FAS research is the study of complex carbohydrates called glycoconjugates. Alcohol-induced perturbations in the integrity of these glycoconjugates may affect a wide range of cellular processes, such as cell to cell interaction, cellular adhesion, cell recognition, immune functioning, and tissue integrity, thus causing developmental abnormalities.

Given the rapid and significant changes in mental and physical states that occur during adolescence, it is possible that alcohol can have profound effects on physiological, social, and interpersonal development during adolescence. Alcohol-induced disruption of the acquisition of new knowledge and skills can have significant repercussions on learning and behavior. Animal models are being developed to determine whether certain functions or structures of the adolescent brain are more vulnerable than the adult brain to alcohol's chronic and acute effects. The effects of alcohol on normal hormonal activation during puberty, and whether alcohol-induced hormonal changes can affect both brain function and the development of gender differences in behavior and physiology, will also be investigated.

Youthful perceptions concerning the proper use of and the effects of alcohol influence their drinking behavior. Parents, schools, police, primary-care physicians, and other community groups set and enforce norms concerning alcohol use by youth. Peer groups also set and enforce drinking use, thus establishing normative behavior. NIAAA is especially interested in investigating norm-setting and norm enforcement by these groups as a means of reducing youthful alcohol consumption.

HEALTH SERVICES RESEARCH

Research on how treatment and prevention interventions are delivered and their effectiveness is of paramount importance to NIAAA's mission. Multidisciplinary in scope, the NIAAA program funds studies on the impact of organization, financing, management, and the delivery of alcohol-related health services on service accessibility, quality, utilization, cost, and outcome.
Alcohol health services research will play a critical role in defining essential alcohol-related health care benefits during the revamping of our Nation's health care system.

Financing and reimbursement studies will assess the impact of public policy on financing arrangements and, in turn, the impact of these arrangements on the availability, costs, and effectiveness of alcohol-related health services. Effectiveness studies will assess outcomes of prevention and treatment services and identify those aspects of service delivery that improve outcomes. Identifying the specific factors, both personal and programmatic, that influence treatment outcome is a priority. Existing governmental initiatives offer numerous opportunities for evaluations of the effectiveness of public policy based prevention services for alcohol problems. For example, studies evaluating the effectiveness of sentencing alternatives, such as alcoholism treatment, deferred sentencing, and administrative license revocation, for drunk driving arrests will help policy-makers design and implement effective programs that reduce the occurrence of drunk driving.

Making treatment and prevention programs available to people who need them is a fundamental objective for alcohol researchers, clinicians, and policy-makers. Researchers are analyzing a number of barriers that may limit access to treatment or prevention services. Barriers that limit access to care may be psychological, financial, or physical. Other barriers to access may be the availability, supply, and distribution of prevention and treatment programs. The unique requirements of special populations--women, youth, minorities, and elderly--affecting their accessibility to treatment and prevention programs will also be assessed.

As our nation tries to harness the escalating costs of health care, cost effectiveness studies are becoming an essential component of research on alcoholism treatment and prevention intervention. The goal of cost-effectiveness studies is to identify the most effective treatment and prevention services that can be offered at reasonable cost. Studies in utilization, cost, and cost-offset focus on measuring and analyzing the use and costs of alcohol-related prevention and treatment services. Cost-offset studies will determine whether the costs of prevention and treatment services are balanced by subsequent reductions in health care expenses.

MEDICATIONS DEVELOPMENT

Excessive consumption of alcohol results in many deleterious effects, such as psychological and physical dependence, liver cirrhosis, pancreatitis, gastritis, cardiovascular disorders, certain cancers, and immune, endocrine, and reproductive illnesses, and alcohol-related dementia. The goal of NIAAA's medications development program is to obtain medications that 1) directly palliate or even reverse the organ damage caused by alcohol and 2) block alcohol-seeking behavior.

Research on medications to treat alcoholic liver and other alcohol-related, end-organ diseases will be supported. Effects of alcohol on cytokine production, cell adhesion, chemotaxis, and inflammatory processes will be delineated and the study of glycoconguates may identify mechanisms underlying tissue damage. Recent studies have shown serotonin re-uptake inhibitors can improve memory to a clinically meaningful degree in some patients with alcohol-induced amnesia. Additional bio-behavioral studies providing clues for the development of the pharmacologic management of alcohol-induced brain damage are also planned.

Protracted withdrawal from alcohol can be life-threatening and may lead to relapse. In addition, a significant number of people die each year from alcohol overdoses, primarily from respiratory depression. Basic research in these two areas is planned so that specific pharmacologic interventions can be designed.

Research on the role of neuropeptides, sex steroids, cholecystokinin, HPA hormones, environmental cues, and the endocrine system on alcohol-seeking behavior may provide the necessary information for developing pharmacologic agents that will attenuate alcohol craving and block its euphoric effects. Naltrexone, an opiate antagonist, has already shown clinical promise as an agent that reduces craving for alcohol. Additional clinical studies are planned to better describe the usefulness of naltrexone and another promising opiate antagonist, nalmefene. Gene-disruption experiments will be used to further delineate the role of neuroreceptor systems and receptor subtypes in attenuating alcohol drinking behavior.

Genetic factors predisposing to alcoholism will be studied in humans. Identification of the genes and gene products influencing alcohol consumption, sensitivity, tolerance, dependence, or other relevant responses to alcohol in humans will provide potential targets for pharmacological intervention. A major goal is to determine if human homologs of animal QTLs (quantitative trait loci) exist and whether humans carry alterations in any of these genes. Genetic analyses of more complex alcohol-related animal behaviors that provide closer models of human alcoholism, such as, inelastic demand for alcohol, tendency to increase alcohol consumption after stress, and susceptibility to pharmacological reinforcing effects of alcohol are of great importance.

PREVENTION

Research is underway to determine the family, socio-cultural, legal, and other environmental triggers that can interact with individual vulnerability and result in alcohol abuse and alcoholism. Data from this research will shed new light on when to intervene and prevent the development of alcohol disorders. Advances in study designs, methodologies, and technologies, such as, computer modeling make increasingly precise evaluation of interventions possible.

Despite general population declines in drinking during pregnancy, FAS remains the leading preventable cause of mental impairment; current U.S. incidence is estimated at 1 to 3 infants per 1,000 live births. FAS prevention efforts will draw upon previously successful didactic and clinical interventions to develop multi-strategy approaches combining media messages with relevant cultural influences.

NIAAA will maintain a focus on preventing alcohol-related problems in youth, including studies that examine the enforcement of laws, regulations and policies affecting youth access to alcohol; and studies that focus on the acceptability of youth alcohol use, and the development of attitudes and expectancies regarding alcohol use. Interventions will be developed that influence adolescent decision-making regarding alcohol use and associated risk behaviors. The family's protective role, as well as, the role of domestic violence on the development of future alcohol problems will be studied. Additional research will explore the effects of norms and norm-setting on youthful alcohol consumption.

Research on the interaction of alcohol with environmental influences includes examining: the economic influences that affect decisions to drink alcohol; the relationship of alcohol and violence; alcohol abuse among the elderly, non-traffic, alcohol-related injuries; and the influence of alcohol on high-risk sexual practices which may lead to infection with HIV.

MINORITY HEALTH

The 1990 National Household Survey indicates that 68.3 percent of whites, 64.5 percent of Hispanics, and 55.6 percent of African-Americans used alcohol in the past year. Differing patterns of alcohol use and abuse underlie these seemingly similar percentages. Some minority groups seem to exhibit a higher prevalence of alcohol-related problems than whites, despite similar or lower rates of consumption.

Certain minority groups may possess genetic traits that either predispose them toward alcoholism or protect them from becoming alcoholic. Few such traits have so far been discovered, although the flushing reaction, found in the highest concentrations among individuals of Asian ancestry, is one example.

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NIAAA-sponsored researchers who are exploring alcohol problems in minorities are striving to discover the genetic and environmental factors that may place minorities at risk for, or protect them from, alcohol problems; they are also working to generate effective alcoholism treatment and prevention strategies. Expanded understanding of the genetic mechanisms for alcoholism and its pathologies will apply to the general population, as well. Knowledge from these studies will lay the foundation for conceiving prevention and early intervention approaches aimed at high risk individuals, and will open avenues for developing biological therapies that compensate for genetic vulnerability.

National Institute on Alcohol Abuse and Alcoholism

Intramural Research

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part C Section 464H. 1994 Authorization: Such sums as necessary.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
112	$19,991,000	113	$20,203,000	109	$20,224,000	-4	+$21,000

The NIAAA Intramural Research program conducts a comprehensive research program through a full range of studies that not only define the parameters of alcohol abuse and alcoholism, but explore the diverse fields of cause, diagnosis, treatment, and prevention as well as the biological and psychosocial factors that predispose people to alcohol abuse. Its clinical research studies are located on the NIH campus while the basic research activities are located in the Flow Laboratory and Park Building in Rockville.

Funding for this activity during the last 5 years has been as follows:

	Amount	FTE
FY 1990	$16,820,000	102
FY 1991	17,193,000	97
FY 1992	17,973,000	106
FY 1993	19,991,000	112
FY 1994	20,203,000	113

Rationale for the Budget Request

The FY 1995 request for intramural research is $20,224,000, an increase of $21,000 over the FY 1994 appropriation of 20,203,000.

Two particular areas will be emphasized in NIAAA's intramural program in 1995: impulsivity and risk taking behavior and nutrition and alcoholism.

Impulsivity or behavioral disinhibition and high levels of risk-taking behavior are associated with people who become alcoholic early in life. Impulsivity may be associated with random, unprovoked violent behavior, and high-risk sexual behavior that can lead to infection with HIV. Frontal lobe damage in humans often leads to behavioral disinhibition and cerebrospinal fluid (CSF) levels of 5-HIAA, the major metabolite of the brain neurotransmitter serotonin, are reduced in individuals with frontal lobe damage and those with a history of impulsive behavior. A variation in a gene has been discovered which associates with low CSF 5-HIAA and a history of suicide attempts in impulsive alcoholic offenders. As other such genes are found, genetic and behavioral studies will be carried out on non-human primates to discover the effects of these variations.

Recent findings may provide clues for treating impulse control disorders of children. Levels of CSF 5-HIAA were found to be lower in adolescents who had a history of childhood attention deficit and conduct disorders. Parallel findings have been observed in studies of adolescent male monkeys, which may provide an appropriate animal model for human antisocial behaviors. Positron emission tomography (PET) imaging will be used to view the areas of the brain which use serotonin and to visualize differences among human subjects. Molecular biology techniques will be applied to elucidate how genetic variations affect the interactions of neurons, serotonin, and alcohol.

Excessive alcohol use disrupts normal body functioning by causing deficiencies in vital nutrients. Nutritional needs during pregnancy are ten to thirty percent greater than normal. Not only can nutritional deficiencies of an alcoholic mother adversely affect the nutrition of the fetus, but alcohol can also restrict nutrition flow to the fetus. Researchers have recently shown in human alcoholics and animal models, that alcohol abuse leads to a loss of polyunsaturated lipids (fats) from a variety of tissues. Such losses are believed to be related to the tissue damage that occurs in almost every organ system in alcoholics, but particularly in the liver and brain. They have demonstrated a highly specific loss of the major polyunsaturated fatty acid, DHA, in nervous system tissues in cats and rhesus monkeys who were given a "barely adequate diet," such as may be common in alcoholics. These results suggest that alcohol abuse may have a similar effect on the nervous system in humans. The physiologically harmful effects of a loss in DHA include a deficiency in neurological development. Due to inadequate DHA, these neural deficits would likely occur in alcoholics and in infants exposed to alcohol in utero. An intramural clinical project will study the neurological development in infants receiving a formula supplemented with DHA.

National Institute on Alcohol Abuse and Alcoholism

Research Management and Support

Authorizing Legislation: Public Health Service Act, Title III, Part A Section 301, Title IV, Part A Section 464H. 1994 Authorization: Such sums as necessary.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
142	$12,969,000	131	$12,930,000	128	$13,042,000	-3	+$112,000

The Research Management and Support activity supports overall management, planning, policy development, and coordination of the scientific programs and administrative functions of the Institute. Staff provide scientific direction, develop program announcements, support and monitor funded research projects, manage the review and award of grant and contract applications, organize conferences and related activities to promote new initiatives, develop alcohol-related policy analyses, and disseminate research results through a variety of publications, special reports, data systems, and other scientific documents.

Funding for this activity during the last 5 years has been as follows:

	Amount	FTE
FY 1990	$10,227,000	125
FY 1991	11,129,000	135
FY 1992	12,180,000	135
FY 1993	12,969,000	142
FY 1994	12,930,000	131

Rationale for the Budget Request

The FY 1995 request for research management and support is $13,042,000, an increase of $112,000 over the 1994 appropriation.

This activity has strengthened the alcohol research base by supporting: 1) The organization and coordination of workshops for researchers and clinicians in the alcohol field to identify, define, and present the latest research on basic and clinical issues such as fetal alcohol studies, neurobiology of alcohol addiction, alcoholism treatment, and neuroimaging in alcohol research; 2) The dissemination of research findings and information through journals, bulletins, the ETOH (computer) database, the NIAAA Alcohol Thesaurus, and scientific exhibits and conferences; 3) The procurement of a large private-sector database of health insurance claims information.

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Salaries and other operating costs included in the 1995 request are for staff who provide scientific direction and technical expertise in the development and implementation of the Institute's program as well as administrative support in areas of grant monitoring and review, management analysis, planning, budget, and personnel.

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director..................	8	7	8
Office of Planning and Resource Management..........................	46	41	39
Office of Scientific Affairs............	23	24	22
Office of Policy Analysis...............	5	5	5
Division of Clinical and Prevention Research...................	28	25	25
Division of Basic Research..............	17	16	16
Division of Biometry and Epidemiology...	16	13	13
Division of Intramural Clinical and Biological Research...................	111	113	109
Total, NIAAA........................	254	244	237

	Average GS/GM Grade
1989....................................	10.4
1990....................................	10.4
1991....................................	10.4
1992....................................	10.6
1993....................................	10.6
1994....................................	10.8

Note: The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resouces

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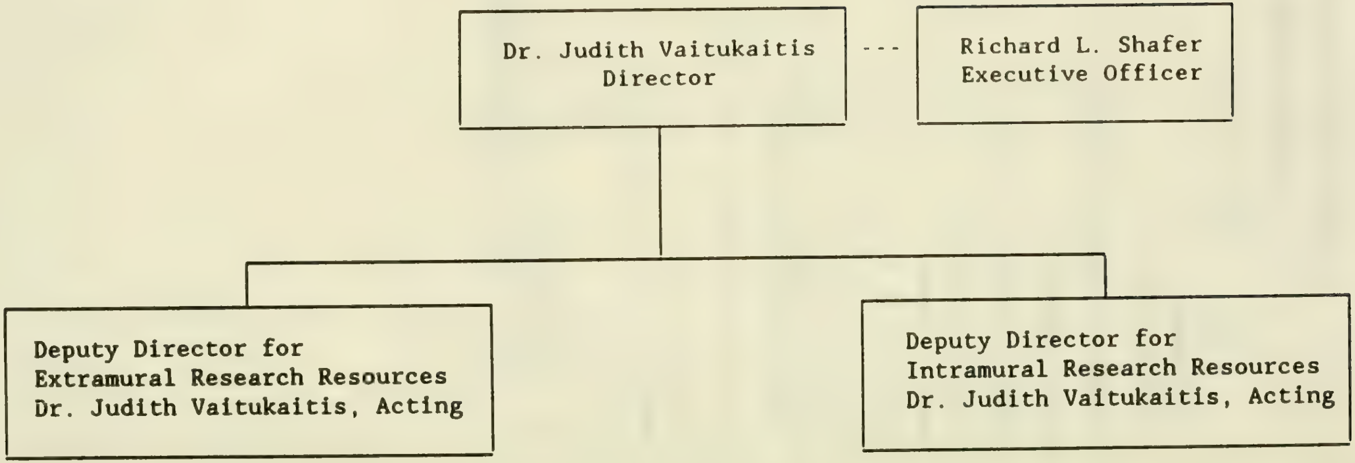
NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Organization Structure



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Extramural Research Resources
Dr. Judith Vaitukaitis, Acting

Deputy Director for
Intramural Research Resources
Dr. Judith Vaitukaitis, Acting

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

For carrying out section 301 and title IV of the Public Health Service Act with respect to research resources and general research support grants, [$331,915,000] $286,394,000: *of which $3,678,000 shall not become available for obligation until September 19, 1995.* Provided, That none of these funds shall be used to pay recipients of the general research support grants program any amount for indirect expenses in connection with such grants. (Department of Health and Human Services Appropriation Act, 1994.)

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Language Analysis

Language Provision	Explanation
"...of which $3,678,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation................	$315,251,000	$331,915,000	$286,394,000
Section 511 reduction........	-2,522,000	---	---
Section 513 reduction........	-26,000	---	---
Section 216 S & E reduction..	-235,000	---	---
Subtotal, adjusted appropriation...........	312,468,000	331,915,000	286,394,000
Real transfer for tuberculosis research.....	+189,000	---	---
Comparable transfer to the Office of AIDS Research for HIV Activities........	-50,881,000	-61,383,000	
Subtotal, adjusted budget authority...............	261,776,000	270,532,000	286,394,000
Unobligated balance brought forward..................	---	---	---
Recovery of prior year balances..................	---	---	---
Unobligated balance available end of year.....	---	---	---
Unobligated balance, lapsing..................	-22,000	---	---
Total, obligations........	261,754,000	270,532,000	286,394,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1993 -- $4,202,000; and FY 1994 -- $5,283,000; and FY 1995 -- $5,283,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	45	$8,149,000	54	$10,592,000	60	$12,240,000
Admin. suppl	--	50,000				
Competing						
Renewal	7	1,685,000	21	4,158,000	22	4,363,000
New	48	4,909,000	37	3,584,000	47	5,564,000
Supplemental	--	---	--	---	--	---
Subtotal competing	55	6,594,000	58	7,742,000	69	9,927,000
Subtotal, res. proj	100	14,793,000	112	18,334,000	129	22,167,000
Research Centers:						
Clinical research	75	100,226,000	75	101,788,000	75	105,982,000
Biomedical research technology	57	38,787,000	58	40,303,000	62	44,311,000
Comparative medicine program	25	34,119,000	21	32,280,000	21	33,161,000
Biological models and materials research	6	1,807,000	5	1,424,000	5	1,424,000
Research centers in minority institutions	18	20,971,000	18	21,244,000	18	22,306,000
Subtotal, research centers	181	195,910,000	177	197,039,000	181	207,184,000

Other research:						
Research career programs.........	14	988,000	15	983,000	15	983,000
Biomedical research support......	46	17,221,000	46	17,194,000	50	18,194,000
Other research related...........	73	12,518,000	63	10,228,000	65	10,593,000
Subtotal, other research.....	133	30,727,000	124	28,405,000	130	29,770,000
Total, research grants............	414	241,430,000	413	243,778,000	440	259,121,000
Training:						
Individual awards:						
Noncompeting..................	2	55,000	-	---	-	---
Competing.....................	1	35,000	2	50,000	2	51,000
Subtotal, individual.............	3	90,000	2	50,000	2	51,000
Institutional awards:						
Noncompeting..................	54	1,859,000	77	2,620,000	77	2,657,000
Competing.....................	23	734,000	--	---	--	---
Subtotal, institutional..........	77	2,593,000	77	2,620,000	77	2,657,000
Total, training..................	80	2,683,000	79	2,670,000	79	2,708,000
Research and development contracts	11	4,740,000	9	4,655,000	9	4,655,000
Facilities construction...........		---		7,000,000		7,000,000
	FTEs		FTEs		FTEs	
Research management and support.........................	108	12,923,000	102	12,429,000	100	12,910,000
Total............................	108	261,776,000	102	270,532,000	100	286,394,000
Clinical Trials................		(36,329,000)		(36,941,000)		(38,512,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Summary of Changes

1994 Estimated budget authority	$270,532,000
1995 Estimated budget authority	286,394,000
Net change	+15,862,000

	1994 Current Estimate Base		Change from Base	
	(FTEs)	Budget Authority	(FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Research Management & Support				
a. Within grade increases	---	$5,884,000	---	+$74,000
b. Annualization of 1994 pay raise	---	5,884,000	---	+48,000
c. One less day of pay	---	5,884,000	---	-20,000
d. 1995 pay increases	---	5,884,000	---	+71,000
e. Federal Employees Compensation Fund	---	24,000	---	+5,000
f. FTS rate increase	---	90,000	---	+1,000
g. DHHS Working Capital Fund	---	150,000	---	+1,000
h. Payment for Centrally Furnished Services	---	3,871,000	---	+314,000
i. Service & Supply Fund	---	963,000	---	+23,000
j. Increased costs of supplies and materials	---	1,711,000	---	+52,000
Subtotal	---		---	+569,000
B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	54	10,592,000	+6	+1,648,000
b. Competing	58	7,742,000	+11	+2,185,000
Total	112	18,334,000	+17	+3,833,000
2. Research centers	177	197,039,000	+4	+10,145,000
3. Other Research	124	28,405,000	+6	+1,365,000
4. Research Training		2,670,000		+38,000
5. Research & Development Contracts		4,665,000		---
6. Facilities Construction		7,000,000		---
Subtotal, extramural			+27	+15,381,000
	(FTEs)		(FTEs)	
7. Research Management and Support	102	12,429,000	-2	-88,000
Subtotal				+15,293,000
Total changes				+15,862,000

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment..	102	100	-2
Full-time equivalent of overtime and holiday hours.............	2	2	---
Average ES salary..................	$107,300	$111,807	+$4,507
Average GM/GS grade................	9.8	9.8	---
Average GM/GS salary...............	$46,737	$47,935	+$1,198
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)....................	$77,607	$77,607	---
Personnel compensation:			
Full-time permanent..............	$4,364,000	$4,366,000	+$2,000
Other than full-time permanent....	333,000	234,000	-99,000
Other personnel compensation......	156,000	177,000	+21,000
Total, personnel compensation.....	4,853,000	4,777,000	-76,000
Personnel benefits.................	816,000	887,000	+71,000
Benefits for former personnel.......	5,000	5,000	---
Travel and transportation of persons..........................	105,000	144,000	+39,000
Transportation of things...........	20,000	20,000	---

	1994 Appropriation	1995 Estimate	Increase or Decrease
Rent, communications, and utilities.	175,000	175,000	---
Printing and reproduction..........	135,000	135,000	---
Other services:			
Consultant services..............	100,000	100,000	---
Other Services....................	1,216,000	845,000	-371,000
Purchase from Govt. Accts.........	4,799,000	5,692,000	+893,000
R&D Contracts.....................	4,655,000	4,655,000	---
Supplies and materials.............	80,000	75,000	-5,000
Equipment..........................	125,000	55,000	-70,000
Grants, subsidies & contributions...	253,448,000	268,829,000	+15,381,000
Total............................	270,532,000	286,394,000	+15,862,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NCRR

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	4,364	4,364	4,366	2
11.3	Other than full-time permanent	333	333	234	(99)
11.5	Other personnel compensation	156	156	177	21
11.8	Special personnel services payments	0	0	0	0
11.9	Subtotal, personnel compensation	4,853	4,853	4,777	(76)
12.1	Civilian personnel benefits	816	816	887	71
13.0	Benefits for former personnel	5	5	5	0
	Subtotal Pay Costs	5,674	5,674	5,669	(5)
21.0	Travel and transportation of persons	105	105	144	39
22.0	Transportation of things	20	20	20	0
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	175	175	175	0
24.0	Printing and reproduction	135	135	135	0
25.0	Other Services	6,115	4,585	5,107	522
26.0	Supplies and materials	80	80	75	(5)
	Subtotal non-pay costs	6,630	5,100	5,656	556
	Total Administrative Costs	12,304	10,774	11,325	551

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Significant Items in House and Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1994 House Report	
Biological Models	
1. The House in its report 103-156, page 68, stated, "The Committee is pleased with the program developed by NCRR to generate marine models for use in biomedical research. Within the increase provided for NCRR, the Committee encourages the expansion of research to identify and use marine organisms as biomedical models."	1. Within the increase provided by the House Committee, the NCRR provided an increase of approximately $500,000 to expand research to identify and use marine organisms as biomedical models.
IDeA Grants	
2. The House in its report 103-156, page 68, stated, "The Committee has been pleased with the development of the Institutional Development Award (IDeA) program to broaden the geographical distribution of NIH funding for biomedical research, which is similar to the EPSCoR program supported by the National Science Foundation. The Committee encourages NCRR to increase its support for the IDeA program."	2. Within the funds provided by the House Committee to the NCRR, $785,000 was set aside for support of the IDeA program, an increase of 4.7 percent over the level of funding in 1993.

1994 Senate Report

Extramural Construction	Action Taken or to be Taken
1. The Senate in its report 103-143, page 118, stated, "The Committee concurs with the criteria and urges the Director to consider the factors stated in the section in determining the criteria for consideration of extramural construction proposals. The Committee is particularly supportive of expanding the capacity of established pediatric research facilities affiliated with a children's hospital, such as the Children's Hospital of Philadelphia, to broaden the scope of genomic research into various cancers of childhood, pediatric tumors, and congenital heart disease."	1. In the Request for Applications recently published for the extramural construction program, applications were specifically encouraged in the area of pediatric genomics.
IDeA Grants	
2. The Senate in its report 103-143, page 118, stated, "The Committee directs the NCRR to increase its funding for the IDeA Program over the 1993 level. The Committee also directs that all States designated by the EPSCoR Program in the National Science Foundation be included in the NIH program. Because the State-based improvement mechanism is essential, State EPSCoR committees shall submit institutional development award applications. These applications should be evaluated by NIH to determine the effectiveness of the strategies to enhance a State's competitive base for NIH funding. The Committee encourages the NIH Director to consult with the NSF Director to ensure coordination of the two programs."	2. Within the funds provided by the Senate and appropriated, the NCRR set aside $785,000 for the IDeA program, an increase of 4.7 percent over the 1993 level. In the recently published Request for Applications for this program, all EPSCoR states were specifically listed as eligible and encouraged to apply. One criterion for evaluation of applications is the effectiveness of the strategies to enhance a State's competitive base for NIH funding.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation......	Section 301	42s241	Indefinite	$267,862,000	Indefinite	$283,686,000
National Center for Research Resources......................	Section 479,480	42s287 287a,300a, and 5s332	Indefinite		Indefinite	
National Research Service Awards	Section 487	42s288	$400,000,000	2,670,000	Such sums as necessary	2,708,000
Total Budget Authority........				270,532,000		286,394,000

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1985	$247,528,000	$305,331,000 2/	$305,298,000	$304,025,000
1986	263,040,000	304,579,000 3/	305,739,000	305,667,000
1986 Sequester				-13,144,000
1987 4/	234,192,000	317,826,000	319,924,000	322,860,000
1988	280,415,000	346,652,000 5/	367,415,000	368,153,000
1989	319,977,000 6/	355,767,000 7/	367,987,000	358,608,000 8/
1990	263,313,000 9/	356,128,000	362,253,000	353,734,000 10/
1991	319,151,000	355,962,000	331,629,000	335,255,000 11/
1991 Sequester				-4,000
1992	320,975,000	309,200,000	317,227,000	314,213,000 12/
1993	330,231,000	311,207,000	315,551,000	312,468,000 13/
1994	327,887,000	328,915,000	332,915,000	331,915,000
1995	286,394,000 14/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes $775,000 in NRSA training programs not considered.

3/ Excludes $1,029,000 in NRSA training programs not considered.

4/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread funding among the institutes, including $6,142,000 for the Division of Research Resources.

5/ Does not include funding for AIDS research which was consolidated at the Secretary's level.

6/ The 1989 request excludes funds for AIDS research and education ($38,010,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

7/ Excludes $2,220,000 in NRSA training programs not considered.

8/ Reflects a 1.2% reduction ($4,356,000) and a reduction of $23,000 as a result of improved procurement practices from the appropriated level of $362,987,000 as required by P.L. 100-436 Sections 517 and 215 respectively.

9/ The 1990 request excludes funds for the National HIV program ($44,643,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

10/ Excludes enacted administrative reductions of $16,000 for procurement savings; $344,000 for extramural salary cap and $97,000 for salaries and expenses.

11/ Excludes enacted administrative reduction of $8,541,000.

12/ Includes enacted administration reduction of $669,000, and enacted recision of $338,000.

13/ Reflects a .8% reduction ($2,522,000), a S&E reduction ($235,000), and Consultant Services reduction ($26,000).

14/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Clinical research........ .	–	$95,585	–	$102,904	–	$101,232	–	$103,122	–	$107,316	–	$4,194
Biomedical research technology..	–	40,210	–	45,555	–	49,388	–	52,906	–	60,252	–	7,346
Comparative medicine program..................... ..	–	48,775	–	51,186	–	50,629	–	45,878	–	46,827	–	949
Biomedical research support.....	–	63,686	–	22,519	–	18,062	–	18,804	–	20,094	–	1,290
Biological models and materials research... ..	–	7,739	–	8,035	–	8,571	–	9,149	–	9,689	–	540
Research centers in minority institutions.....	–	19,909	–	21,167	–	20,971	–	21,244	–	22,306	–	1,062
Research facilities improvement..............	–	—	–	—	–	—	–	7,000	–	7,000	–	—
Unobligated balances brought forward...........	–	—	–	—	–	—	–	—	–	—	–	—
Unobligated balances available end of year...	–	—	–	—	–	—	–	—	–	—	–	—
Research management and support...................	98	12,442	104	12,781	108	12,901	102	12,429	100	12,910	-2	12,781
Subtotal, obligations......	98	288,345	104	264,147	108	261,754	102	270,532	100	286,394	-2	15,862
Unobligated balance lapsing..........................	–	+31	–	+15	–	+22	–	—	–	—	–	—
Total, budget authority...		288,377		264,162		261,776		270,532		286,394		15,862

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs included in the Office of AIDS Research.

Justification

National Center for Research Resources

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
108	$261,776,000	102	$270,532,000	100	$286,394,000	-2	+$15,862,000

General Statement

The document provides justification for the FY 1995 Non-AIDS activities of the National Center for Research Resources. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

The National Center for Research Resources (NCRR) serves as a "catalyst for discovery" by creating and providing critical research technologies and shared resources. This infrastructure underpins biomedical research and enables advances that improve the health of our Nation's citizens.

Biomedical researchers supported by the Institutes and Centers of the National Institutes of Health require a broad array of tools, technologies and materials critical to their research efforts. From the animal or nonanimal models required for research on diseases and disabilities, to the biomedical technology and instrumentation necessary to elucidate cellular and molecular structure, to the clinical settings in which to conduct clinical trials of new therapies, biomedical researchers must have access to the necessary resources in order to continue to expand and progress.

The NCRR has the unique mission at the National Institutes of Health of developing critical research technologies and providing multidisciplinary resources to the biomedical investigators across the spectrum of research activities supported by the NIH. This mission has four major facets:

(1) Develop technologies and create resources that are accessible and responsive to the research needs of the biomedical research community. To meet these needs the NCRR must keep abreast of evolving trends in basic and clinical research so that resources will greatly facilitate that research.

(2) Provide shared clinical, primate and biotechnology resources for use by investigators. These resources, primarily centers, serve more than 7,000 researchers, supported through well over $1 billion of categorical Institute funds. Without these shared resources, the Institutes would be required to provide resources on a case-by-case basis, at a greatly reduced efficiency and greatly increased cost.

(3) Develop quick, flexible approaches to new and emerging biomedical research needs and opportunities. Such innovations often involve high-risk research that may have high payoffs.

(4) Strengthen the nation's biomedical research infrastructure through programs to develop and enhance the capacity of minority institutions and centers of emerging excellence to participate in biomedical research, to increase the exposure of K-12 students and their teachers to the life sciences, to improve the condition of research animal facilities, and to construct or renovate facilities for biomedical and behavioral research.

The NCRR supports sophisticated instrumentation and technology, animal models for studies of human disease, and clinical research environments, and develops the research capacity for underrepresented groups. Present and future programs emphasize marine biotechnology, computer-aided drug design, teletechnologies, structural biology, molecular as well as gene-derived therapies and vaccine development for current and emerging public health threats.

The NCRR is a key player in addressing pressing research issues such as access to state-of-the-art technologies and instrumentation; containment of the escalating costs of highly sophisticated clinical research; development of specialized research models including vertebrate, invertebrate and non-animal models; remedying the shortage of independent clinical investigators and the underrepresentation of minority investigators.

The President's appropriation request of $286,394,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Center for Research Resources for the last five years is as follows:

	Amount	FTEs
FY 1990	$291,009,000	100
FY 1991	288,377,000	103
FY 1992	264,162,000	109
FY 1993	261,776,000	108
FY 1994	270,532,000	102

Purpose and Method of Operation

The National Center for Research Resources funds the development, support and provision of critical research resources and technologies, as well as the enhancement of research capacity, through its seven extramural programs. Most of these are involved across the whole range of the Center's mission, utilizing a variety of methods of institutional and investigator support. Resource centers constitute the largest proportion of the Center's budget, and support nationwide networks of centers for conducting clinical research, for accessing state-of-the-art biomedical research technologies, and for conducting research in nonhuman primates, other mammalian or nonmammalian models. The centers mechanism also helps enhance the research capacity of minority institutions throughout the U.S. Research project grants and resource-related research grants support innovative development of resources, including animal and other models and biotechnology. Through other support mechanisms, NCRR provides state-of-the-art instruments to be shared by several NIH-supported researchers, as well as an array of biological materials for use by investigators. NCRR also funds improvement of animal facilities, career development, and programs to encourage careers for underrepresented groups in science. NCRR provides training for research veterinarians and young clinical investigators, including minority investigators. Research contracts provide a variety of resources to individual investigators. The construction program provides for enhancement of the research facilities of institutions.

Overall Budget Policy

The FY 1995 budget request for the National Center for Research Resources is $286,394,000, an increase of $15,862,000 over the FY 1994 level of $270,532,000. Incremental funding will be provided for high performance computing, breast cancer research, Institutional Development Awards, Science Education Partnership Awards, shared instrumentation, and development of clinical research infrastructure, especially at minority institutions.

In FY 1995, the NCRR will support 60 noncompeting research project grants (RPGs) and 69 new or competing RPGs. The NCRR will support 181 research centers, an increase of $10,145,000 over the FY 1994 level. NCRR will maintain support to 75 general clinical research centers, 7 regional primate research centers, 14 laboratory animal sciences centers, 5 biological models and materials research centers, and 18 research centers in minority institutions. The NCRR will also support 62 biomedical research technology centers, an increase of four centers over the FY 1994 level.

Most activities in the "Other Research" category will be maintained at the FY 1994 level. Awards in the Shared Instrumentaion Grant program will increase by four, and the Minority High School Research Apprentice Program will be funded at a level of $9,353,000. Approximately 15 research career awards will be made, and there will be approximately 65 awards in the other research-related category. The FY 1995 request for research training is $2,708,000, an increase of $38,000 over the FY 1994 level, which will support approximately 77 institutional full-time training positions, and 2 individual fellowships. The budget request for research and development contracts is $4,655,000, the same level as in FY 1994, supporting nine contracts.

The FY 1995 budget request for Research Management and Support is $12,910,000, an increase of $481,000 or 3.9 percent over FY 1994. Approximately 100 FTEs will be supported, two fewer than in FY 1994.

The FY 1995 request will support 129 total research project grants at $22,167,000, an increase of 17 awards and $3,833,000 over the FY 1994 appropriation. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one-time non-recurring costs such as equipment. The growth in the average cost of competing grants from FY 1994 to FY 1995 by 5.2 percent exceeds the Biomedical Research and Development Price Index for NCRR because of the change in mix in the types of grants and the science funded. The NCRR expects to fund more Phase II Small Business Innovative Research grants and to increase the number of program projects funded. In addition, new high performance computing and communications grants will be more expensive than the average grant supported in FY 1994.

National Center for Research Resources

Extramural Research

Authorizing Legislation - Sections 301, 479, 480, and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$248,853,000	$258,103,000	$273,484,000	+$15,381,000

The Extramural Research Programs of the National Center for Research Resources develop and support critical research technologies and shared resources that underpin health-related research to maintain and improve the health of our nation's citizens. These programs support sophisticated instrumentation and technology, animal models for studies of human disease, and clinical research environments, and develop the research capacity for underrepresented groups. NCRR Extramural Programs use funding mechanisms that allow rapid response to unanticipated health research needs. Just as the NCRR has responded to these and other concerns in the past, the Center proposes to undertake new initiatives in anticipation of the NIH's future resource needs.

Funding for the extramural programs of the NCRR during the last five years has been as follows:

	Amount
FY 1990	279,654,000
FY 1991	275,904,000
FY 1992	251,366,000
FY 1993	248,853,000
FY 1994	258,103,000

Rationale for the Budget Request

The FY 1995 budget request for the Non-AIDS extramural research activities of the NCRR is $273,484,000, an increase of 6 percent over the FY 1994 estimate. Incremental funds will be devoted to the expansion of high performance computing, breast cancer research, shared instrumentation, clinical gene therapeutics, institutional development, and science education.

With the FY 1995 extramural request, these funds will provide support for the following activities: Clinical Research, $107,316,000, an increase of $4,194,000 or 4.1 percent over the FY 1994 estimate of $103,122,000; Biomedical Research Technology, $60,252,000, an increase of $7,346,000 or 13.9 percent over the FY 1994 estimate of $52,906,000; Comparative Medicine, $46,827,000, an increase of $949,000 or 2.1 percent over the FY 1994 estimate of $45,878,000; Biomedical Research Support, $20,094,000, an increase of $1,290,000 or 6.9 percent over the FY 1994 estimate of $18,804,000; Biological Models and Materials Research, $9,689,000, an increase of $540,000 or 5.9

percent over the FY 1994 estimate of $9,149,000; Research Centers in Minority Institutions, $22,306,000, an increase of $1,062,000 or 5 percent over the FY 1994 estimate of $21,244,000; and Research Facilities Improvement, $7,000,000, the same as the FY 1994 estimate.

RESOURCES FOR CLINICAL RESEARCH

The National Center for Research Resources supports a national network of clinical research facilities, offering a research infrastructure that includes specialized research nurses, research dietitians, biostatisticians, computer hardware and software systems for data management and analyses, sophisticated laboratories, customized facilities, and other resources vital for inpatient and outpatient research. The General Clinical Research Centers (GCRCs) complement the funding provided to investigators who study cancer, heart diseases, diabetes, reproductive biology, nutrition, rehabilitation, aging, alcoholism, drug addiction, arthritis, infectious diseases, and mental disorders; develop new diagnostic tests and therapies; and investigate scores of other health problems affecting both children and adults. In FY 1992, 7,689 investigators carried out 4,830 clinical research projects involving 29,584 hospital admissions, 85,288 research inpatient days, and 203,323 outpatient research visits. To aid in increasing the number of research physicians, the Center supports clinical research training and career development, including the very successful Clinical Associate Physician (CAP) and the Minority Clinical Associate Physician (MCAP) programs.

In FY 1993, scientists at 19 GCRCs and 10 other institutions concluded the most comprehensive diabetes study ever conducted. The 10-year Diabetes Control and Complications Trial compared the effectiveness of intensive versus conventional treatment regimens in preventing or slowing the progression of complications in patients with insulin-dependent diabetes mellitus. Intensive treatment included three or four insulin injections a day or the use of an insulin pump, four or more blood sugar tests a day, a special diet, an initial hospital stay, and weekly to monthly clinical visits. Patients on conventional treatment followed the standard regimen that included one or two insulin injections a day, daily blood sugar tests, and clinical visits every 3 months. The study showed that intensive treatment slows the onset and progression of long-term diabetes complications such as diabetic eye, kidney, and nerve disease, which are among the leading causes of death and disability in the United States.

The first gene therapy experiment for treating high blood cholesterol was conducted at two GCRCs. Familial Hypercholesterolemia (FH) is an inherited disorder caused by an abnormality in the LDL receptor, a liver protein that removes from the blood the "bad" form of cholesterol that is associated with hardening and narrowing of the arteries, increased risk of heart attacks and strokes, and usually early death. FH individuals in this study first undergo surgery to have a small piece of liver removed. In a special laboratory, the liver cells are exposed to a virus previously made harmless (a recombinant retrovirus) that carries into the cells the gene that produces a normal LDL receptor. These genetically corrected cells are then injected into the same patient and go to the liver. A substantial and sustained reduction in blood LDL cholesterol levels has been observed in the first patients. Other gene therapy studies have begun at several GCRCs, involving therapy for cystic fibrosis, cancer, and Gaucher's disease.

GCRC investigators helped identify a genetic region on chromosome 17 that appears to contain a susceptibility factor for breast cancer in certain families. To provide enough genetic material (DNA) for study, researchers in the GCRC core laboratory stimulated the growth of white blood cells from patients and cultured them. The investigators then screened members of families with a high incidence of breast cancer to identify which women are at high risk. This information should prevent women who are members of breast cancer-susceptible families, but who are found not to carry the gene, from undergoing unnecessary prophylactic mastectomies.

Investigators at a GCRC studied whether the drug captopril could reduce morbidity and mortality after a heart attack (myocardial infarction). The study showed that mortality from all causes was significantly reduced in the captopril group compared with the placebo group. There was a 21 percent reduction in risk of having a major cardiovascular event in the captopril group. The study showed that long-term administration of captopril to patients with asymptomatic left ventricular dysfunction after myocardial infarction resulted in improved survival and reduced morbidity and mortality.

GCRC investigators used a breath test to determine the correct dose of cyclosporine, an immunosuppressive drug required by patients who have received an organ transplant. Cyclosporine and other drugs are metabolized, or broken down, by certain enzymes which are present in different amounts in different individuals. To avoid giving some patients too much cyclosporine—and others too little, physicians can individualize each patient's drug dose based on the person's ability to metabolize the drug. Since cyclosporine and the common antibiotic, erythromycin, are both metabolized by the same enzyme, erythromycin metabolism can serve as a "surrogate" for cyclosporine metabolism. The scientists administered "tagged" erythromycin to patients who were about to receive kidney transplants. Twenty minutes later, the investigators determined how much "tagged" carbon dioxide (a metabolic product of erythromycin) the patients exhaled. From this information, they were able to calculate correct individual cyclosporine doses.

In 1995, the NCRR will place increased emphasis on molecular medicine, including gene therapy, on research involving women and minorities, and on training and career development of young clinical investigators.

BIOTECHNOLOGY RESOURCES

The NCRR funds centers for the development and application of sophisticated technologies that are essential to biomedical research, but not widely available, because of expense or other reasons. These centers are staffed by gifted scientists and engineers who work closely with outside biomedical scientists, industry, and other laboratories to both develop and apply new technological capabilities to cutting-edge biomedical research problems.

Research on magnetic resonance imaging is an area of emphasis that was recently expanded. The extension of this technique into functional imaging has been important for clinical research, since it permits minimally invasive study of organ and tissue function in a timed manner. High performance computing and communication (HPCC) remains a major support area that underlies much of the rest of the biomedical research technology research areas. Image analysis and structural biology depend heavily on advanced computing. The NCRR supports five advanced computing centers, with additional related centers in areas such as advanced graphics and biological modeling. The National Science Foundation and the Advanced Research Projects Agency provide joint support for several of the computing centers, and the Department of Energy provides essential support for three of the biological synchrotron facilities funded by the NCRR. Cooperative linkages with other agencies in support of research technologies are thus continuing and provide cost-effective partnerships for biomedical research.

Each year many Americans receive influenza shots to avoid the general misery and risks of the disease. However, the shots of "killed virus" vaccines don't always work, especially in children and the elderly where multiple shots are often needed to provide immunity. Researchers are using the power of high performance computing to study the structure of the influenza virus, and in particular, the ribonucleic acid packed within the influenza particle's outer shell. By uncovering the linkage and assembly of these structures and determining the role they play in viral activity, the researchers are confident that a live virus vaccine that is safe and significantly more effective can be developed for use in people of all ages.

Muscle contraction is an essential and fundamental characteristic of life forms. Scientists have investigated the basis of muscle contraction since the pioneering demonstration in the 1950's of the essential biochemical components of muscle. Recently the structure of a major component of muscle involved in contraction was determined with the use of synchrotron radiation from NCRR-funded facilities. This structure and the detailed computer model of muscle contraction provided the first detailed molecular model for this key process. The research will have long range impact on the understanding of biological function and disease that affect muscle function.

In FY 1995, the NCRR will expand research project grant support in biomedical engineering. The focus of this initiative will be to apply microfabrication techniques and micro-electromechanical systems to support clinical research, and to improve the efficiency and effectiveness of patient care. These technologies include: indwelling and non-invasive sensors; implantable devices including pumps, actuators, and micromotors; ambulatory monitoring systems; and novel biocompatible materials and tissue interfaces. In addition, NCRR will extend its support of HPCC-related activities and provide funds for an array of activities including support to develop advanced visualization techniques for medical diagnostics and therapeutics to remote sites as well as to develop algorithms for multimodal medical images in real time.

MODELS FOR RESEARCH

The NCRR promotes the development, availability, and accessibility of animal and nonanimal models of human disease. A nationwide network of seven Regional Primate Research Centers provides specialized facilities and experienced personnel to support the development of nonhuman primate models needed to gain improved understanding of human health problems and disease processes. The NCRR also supports projects that assure the health and quality of laboratory animals, determine environmental and welfare requirements of such animals, and establish and maintain special animal colonies for research.

The Center also supports a broad range of model systems, including vertebrates, invertebrates, cell and tissue culture systems, mathematical, and computer and physical models for biomedical research. The NCRR supports centralized facilities or resources that provide critical biological materials such as cell lines, microorganisms, DNA probes, tissues, and lower organisms to the biomedical research community. Marine models are important tools for biologic studies to identify the special genes that act on the early embryo to transform it to a developed animal; those models are invaluable for ascertaining the molecular mechanisms for developmental abnormalities of humans. Centralized resources for biomaterials and models can more efficiently store, catalogue, reproduce, and distribute those needed by hundreds of investigators and save thousands of dollars on individual research grants.

Three out of every four adult Americans will eventually experience gum disease. It is the leading cause of tooth loss after childhood. Recently, investigators have developed a killed-bacteria vaccine that slows gum deterioration in cynomolgus monkeys. Researchers are now evaluating other candidate vaccines to find one that prevents bacterial growth, associated gum disease, and bone loss. These findings will have direct application to this disease in humans.

Cryptosporidiosis, a disease caused by an intestinal protozoal parasite, is a significant cause of acute gastrointestinal distress and diarrhea. The response of guinea pigs to experimental inoculation with the organism has shown they are useful models for studying the immune response to this parasite. Investigators also have begun experiments to determine if the polymerase chain reaction (PCR), a technique for detecting the presence of specific DNA, can help detect and quantify cryptosporidial shedding in infected guinea pigs. Preliminary experiments show that DNA from purified cryptosporidia is detected by this technique.

The great biodiversity of nonmammalian marine organisms is virtually untapped in biomedical research. Research into the basic developmental, cellular, and molecular aspects of marine organisms as model systems will continue to provide information about fundamental biological and physiological processes that are common to organisms from yeast to humans. The NCRR currently funds a resource center to reduce the cost of production and increase the availability of cephalopods (octopus, squid, and cuttlefish) for research and a center to enable the sea snail to be reliably reared and maintained in laboratory culture. The NCRR also supports projects on the development of transgenic aquatic organisms, including fish and sea urchins. Genetic engineering of aquatic organisms will produce interesting and useful models for the study of human genetic disorders.

The NCRR continues to encourage the development of "high connectivity" models. These are organisms or biological systems about which a large body of knowledge is available, resulting in extensive cross information or connection with other systems. High connectivity models provide insight for understanding, diagnosing, and treating human diseases such as cancer and birth defects using the freshwater organism, hydra; a functional study of lobster heart may lead to advances in treating cardiomyopathies such as Marfan's syndrome; an investigation of tumors in clams exposed to herbicides appears to mirror similar tumors in human populations exposed to the same chemicals, and a study of circadian pacemakers (endogenous clocks) in the fruit fly could lead to an understanding of human psychiatric and sleep disorders.

As the U.S. population ages, certain diseases including Alzheimer's and some of the complications of menopause will assume greater importance. The study of such disorders will require animal models of various aged conditions. Some of the traditional "incurable" diseases that afflict our population -- such as multiple sclerosis, amyotrophic lateral sclerosis ("Lou Gehrig's disease"), Huntington's disease, and others -- will continue to be studied. New animal models will be developed to enhance this research.

In FY 1995 the NCRR will expand its National resource capacity for transgenic animals where embryos are preserved, maintained (banked), and distributed; where transgenic animals are produced from the maintained embryos; and where research is conducted on cryopreservation techniques. Transgenic and gene knockout technologies provide invaluable animal models to probe specific genes, including the myriad of here-to-fore unknown protein products of those genes, responsible for normal cell function as well as human disease.

SCIENCE EDUCATION

Started as a Presidential initiative in 1980, the Minority High School Student Research Apprentice (MHSSRA) Program continues as NIH's flagship program for attracting high school students to careers in biomedical research and the health professions. The program provides salaries for students for six to eight week periods during which they gain hands-on research experience in biomedical laboratories. Three years ago, the program expanded to include summer training experiences for K-12 teachers and potential K-12 student-teachers in pre-service education programs.

This year two alumni of the MHSSRA program helped their school win the Academic Technical Bowl, sponsored by the National Society of Black Engineers, for the second consecutive year. The Technical Bowl tests students' knowledge of engineering concepts. Another student was awarded a 4 year, $20,000 National Science Scholarship based on work she did as a MHSSRA Program summer apprentice. A high school science teacher and a university scientist have obtained funding from the M. J. Murdock Charitable Trust to continue a collaboration begun in 1992, when the high school teacher participated in the MHSSRA Program at the university. They studied the melanocyte-stimulating hormone (MSH) receptor and its role in determining susceptibility to malignant melanoma, a form of skin cancer. Results of this research were published in the journal Cell in a paper the teacher coauthored.

The goal of the Science Education Partnership Award (SEPA) is to encourage scientists to work with educators and other organizations to improve student and public understanding of science. In 1991, NCRR and NIH made 24 awards for the development of model programs that span the range of science education. These include a national video education program, a traveling AIDS museum exhibit, biotechnology research experiences for students and teachers, and health promoting outreach programs for inner city and rural communities. The SEPA projects are now well into their third year -- some projects are complete, field-tested, revised, and ready for dissemination to other geographic areas.

In one SEPA project, aimed at K-3 students, educators and scientists have invented a hands-on curriculum which uses insects to teach important concepts in biology and human health. Pilot tests have shown that insects are strong motivators for children. Milkweed bugs are studied to learn about the stages of human growth and development, crickets and grasshoppers to learn about different body parts and worms to learn about growth and nutrition. The curriculum has been tested in four states by over 400 teachers in classes involving 10,000 students, and is now ready for national dissemination.

INFRASTRUCTURE BUILDING AND ENHANCEMENT

High-technology instrumentation is essential for cutting-edge health research and for characterizing biologically important molecules. Rapid technological advances in commercially available instrumentation have made scientists more productive and able to solve problems never addressed before. Begun in 1982, the Shared Instrumentation Grant (SIG) Program provides funds for state-of-the-art instruments such as nuclear magnetic resonance spectrometers, mass spectrometers, computers, x-ray diffractometers and protein and DNA sequencers. These are too costly to purchase with funds from regular research grants. The program is cost-effective since each instrument is shared by an average of 8-10 NIH supported investigators.

The Research Centers in Minority Institutions (RCMI) program expands the Nation's capacity for health research by assisting predominantly minority institutions that offer doctorate degrees in the health or health-related sciences to improve their research infrastructure. The RCMI Program also supports initial funding for the addition of new faculty. A number of these faculty have developed independent research programs in the neurosciences.

RCMI grantee institutions also participate in NIH's human genome initiative and in the development of Regional Research Centers for Minority Oral Health. The latter program is designed to conduct research to improve the oral health of U.S. racial and ethnic minorities, enhance the research capabilities and participation of members of these minorities in oral health research, and develop and strengthen the minority oral health research infrastructure of eligible schools.

Scientists have developed a human immunogenetics laboratory to better define HLA and genes in African Americans, and to better understand the biomedical significance of HLA polymorphisms (i.e., genetic diversity) in disease susceptibility and/or resistance in this population. Both Caucasians and African Americans have a large variety of HLA types, but RCMI-supported investigators have found a greater HLA diversity among African Americans than among Caucasians. In patients with insulin dependent diabetes mellitus (IDDM), they found a specific HLA type associated with IDDM susceptibility. These findings are consistent with the fact that non-insulin dependent diabetes mellitus (NIDDM) occurs more frequently than IDDM in African Americans and other minority populations. Using this HLA resource, researchers also have discovered that HLA genotypes are associated with susceptibility to vitiligo, a skin disorder. In these individuals, vitiligo is an autoimmune disease in which antimelanocyte antibodies circulate in the patient's blood. This immunogenetics laboratory has also enabled investigators to assess the relative risks of genetics and the environment on breast cancer in Black women.

In response to a Congressional initiative, the Institutional Development Award (IDeA) program was implemented in FY 1993. This program provides infrastructure support to institutions in states that have historically low success rates in obtaining NIH research funds. The primary goal of this peer-reviewed program is to increase the probability of sustainable long-term growth of research capability in institutions in these states in order to broaden the geographical distribution of NIH funding for biomedical research. Six awards were made, in the states of Maine, Oklahoma, Idaho, Wyoming, Montana, and South Carolina.

In FY 1994, a new program for construction of extramural research facilities was initiated by the NCRR, to begin to address the need to repair or replace deteriorating biomedical research facilities. This program will continue in FY 1995 at the same level of funding as in FY 1994.

In FY 1995, the NCRR will initiate a program to strengthen clinical research infrastructure at RCMI institutions. This initiative will provide support for development, specialized facilities and core laboratories, epidemiologists, biostatisticians, as well as computer hardware and software and research nurses. This initiative is intended to assure a major role for minority institutions in conducting research to improve the health of minorities as well as to increase the participation of minority investigators in independent clinical research.

National Center for Research Resources

Research Management and Support

Authorizing Legislation - Sections 301, 479, 480, and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
108	$12,923,000	102	$12,429,000	100	$12,910,000	-2	+$481,000

The Research Management and Support activity provides the resources and staff necessary for the program management and scientific direction of the Center and its extramural programs. Scientific and administrative staff work together to plan, develop and carry out these programs in order to provide the extramural research community with the resources essential for the conduct of biomedical research. Administrative and managerial services are provided through the Office of the Director, the Office of Science and Health Reports, the Office of Science Policy, the Office of Grants and Contracts Management, and the Office of Administrative Management (including financial management, human resources management, and information resources management, as well as provision of general administrative services) to all components of the NCRR. The extramural review staff provides policy direction and coordination for all phases of scientific and technical review activities within the NCRR involving research grants, research training grants, and research and development contracts. The extramural program staff provides the planning, development, administration and monitoring of the extramural research programs of the NCRR, and serves in a liaison capacity for applicants, grantees, other components of the NIH, the Department and other science agencies, advisory bodies, and other interested groups in areas related to research resources.

Funding for the Research Management and Support activity program during the past five years has been as follows:

	Amount	FTE
FY 1990	11,355,000	100
FY 1991	12,473,000	103
FY 1992	12,796,000	109
FY 1993	12,923,000	108
FY 1994	12,429,000	102

Rationale for the Budget Request

The FY 1995 budget request for Research Management and Support is $12,910,000. This represents an increase of 3.9 percent percent over FY 1994, which will provide part of the amount required for mandatory increases in costs.

National Center for Research Resources

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Extramural Research Resources................	108	102	100
Intramural Research Resources................	0	0	0
Total , NCRR..............	108	102	100

Average GS/GM Grade

1990.................................	9.9
1991.................................	9.9
1992.................................	9.9
1993.................................	9.8
1994.................................	9.8
1995.................................	9.8

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

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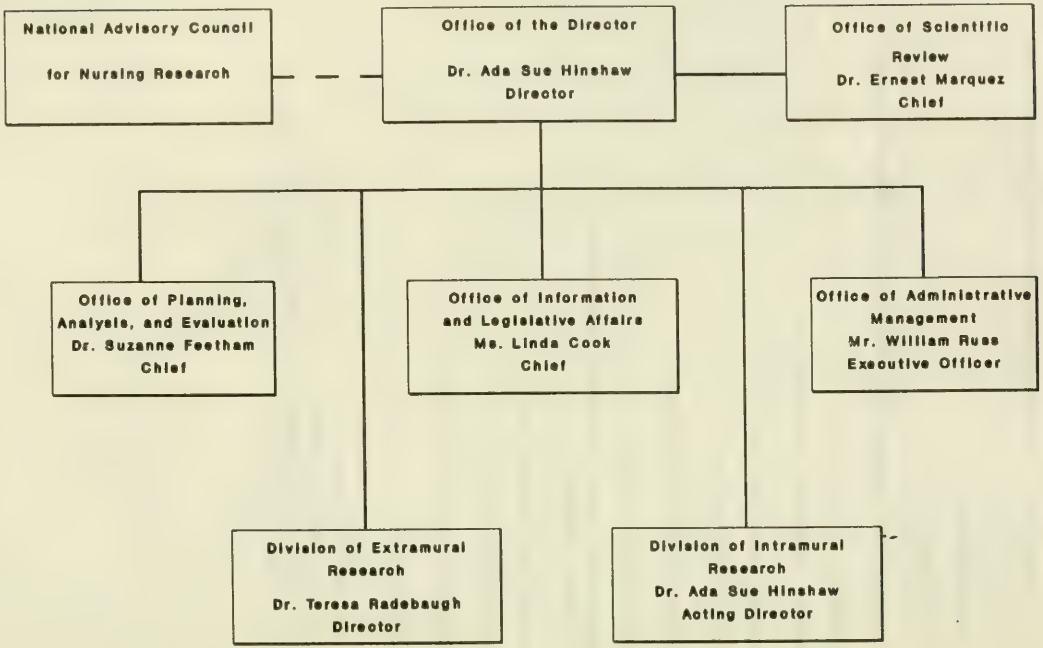
NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to nursing research, [51,018,000] $48,326,000 *of which $555,000 shall not become available for obligation until September 19, 1995.* *(Department of Health and Human Services Appropriation Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Language Analysis

Language Provision	Explanation
"....Provided, That of the funds made available under this heading, $555,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation..................	$48,591,000	$51,018,000	$48,326,000
Section 511 .8% reduction.......	-389,000	---	---
Section 513 consultant services reduction............	-8,000	---	---
Section 216 S & E reduction.....	-75,000	---	---
Subtotal, adjusted appropriation...............	48,119,000	51,018,000	48,326,000
Real transfer from Other Accounts for Tuberculosis Research.........	+377,000	---	---
Comparative transfer to the Office of AIDS Research, NIH for HIV activities............	-2,966,000	-4,444,000	---
Subtotal, adjusted budget authority............	45,530,000	46,574,000	48,326,000
Unobligated balance, lapsing....................	-19,000	---	---
Total obligations...........	45,511,000	46,574,000	48,326,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1993--$3,627,000; FY 1994--$6,620,000; FY 1995--$6,620,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research projects						
Noncompeting..............	106	$22,135,000	113	$25,992,000	98	$23,443,000
Admin. supplemental.......	(14)	344,000	(15)	399,000	(15)	415,000
Competing						
Renewal.................	8	2,730,000	5	1,750,000	8	2,903,000
New.....................	39	7,011,000	21	4,459,000	32	7,161,000
Supplemental............	2	192,000	2	140,000	3	194,000
Subtotal, competing.....	49	9,933,000	28	6,349,000	43	10,258,000
Subtotal, res. proj.........	155	32,412,000	141	32,740,000	141	34,116,000
Research Centers............	7	1,763,000	7	1,799,000	7	1,873,000
Other Research						
Research career program...	15	1,123,000	14	1,213,000	14	1,247,000
Coop. Clin................	---	100,000	---	150,000	---	154,000
Other research related....	10	909,000	14	906,000	14	931,000
Subtotal, other research	25	2,132,000	28	2,269,000	28	2,332,000
Total, research grants........	187	36,307,000	176	36,808,000	176	38,321,000

Training:						
Individual awards:						
Noncompeting..............	81	1,010,000	94	1,449,000	65	1,029,000
Competing.................	38	581,000	23	351,000	52	821,000
Subtotal, individual........	119	1,591,000	117	1,800,000	117	1,850,000
Institutional awards:						
Noncompeting..............	104	2,374,000	86	2,232,000	54	1,441,000
Competing.................	5	124,000	---	---	32	854,000
Subtotal, institutional.....	109	2,498,000	86	2,232,000	86	2,295,000
Total, training..............	228	4,089,000	203	4,032,000	203	4,145,000
Research and development contracts..................	2	80,000	3	655,000	3	673,000
	FTE		FTE		FTE	
Intramural research...........	9	392,000	10	471,000	9	469,000
Research management and support....................	43	4,662,000	42	4,608,000	42	4,718,000
Total........................	52	45,530,000	52	46,574,000	51	48,326,000

NOTE: Includes FTE's associated with HIV Research Activities. Funds to support these FTE's are included in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Summary of Changes

1994 Estimated budget authority	$46,574,000
1995 Estimated budget authority	$48,326,000
Net change	+$1,752,000

Changes:	1994 Current Estimate Base FTEs	1994 Current Estimate Base Budget Authority	Change from Base FTEs	Change from Base Budget Authority
A. Built-in:				
1. Intramural				
a. Within-grade increases		$173,000		+3,000
b. Annualization of January 1994 locality pay increase		173,000		+2,000
c. One less day of pay		173,000		---
d. January 1995 pay increases		173,000		+2,000
e. Payment for centrally furnished services		49,000		+2,000
f. Increased cost of laboratory materials and other supplies		249,000		+7,000
Subtotal				+16,000
2. Research Management and Support				
a. Within-grade increases		2,615,000		+37,000
b. One less day of pay		2,615,000		-11,000
c. Annualization of January 1994 locality pay increase		2,615,000		+12,000
d. January 1995 pay increases		2,615,000		+32,000
e. FECF Unemployment Compensation				+2,000
f. Payment for centrally furnished services		953,000		+39,000
g. Service and supply fund increase		180,000		+35,000
h. Increased cost of laboratory materials and other supplies		860,000		+29,000
i. Increse for FTS				+1,000
Subtotal				+176,000

Summary of Changes--continued

B. Program:	No.	Amount	No.	Amount
1. Research projects grants:				
a. Noncompeting................	113	25,992,000	-15	-2,549,000
b. Admin supplements...........	(15)	399,000	---	+16,000
c. Competing...................	28	6,349,000	+15	+3,909,000
Total..................	141	32,740,000	---	+1,376,000
2. Research centers...............	7	1,799,000	---	+74,000
3. Other research.................	28	2,269,000	---	+63,000
4. Research training..............	203	4,032,000	---	+113,000
5. Research development and contracts..................	3	655,000	---	+18,000
	FTEs		FTEs	
6. Intramural research............	(10)	471,000	-1	-18,000
7. Research management and support	(42)	4,608,000	---	-66,000
Subtotal..............			-1	+1,560,000
Total changes.........				+1,752,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment....	52	51	-1
Full-time equivalent of overtime and holiday hours................	0	0	0
Average ES salary....................	$112,000	$112,000	---
Average GM/GS grade..................	11.7	11.7	---
Average GM/GS salary.................	53,029	53,877	+848
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	61,179	61,179	---
Average salary of ungraded positions.	51,850	52,680	+830
Personnel compensation:			
Full-time permanent.................	$2,019,000	$2,080,000	+$61,000
Other than full-time permanent......	278,000	281,000	+3,000
Other personnel compensation........	---	---	---
Subtotal, personnel compensation.	2,297,000	2,361,000	+64,000
Personnel benefits..................	491,000	506,000	+15,000
Travel and transportation of persons	91,000	76,000	-15,000
Transportation of things............	15,000	15,000	---
Rent, communications and utilities..	90,000	90,000	---
Printing and reproduction...........	70,000	70,000	---
Other services:			
Consulting services...............	230,000	228,000	-2,000
Project contracts.................	655,000	673,000	+18,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Other services....................	123,000	130,000	+7,000
Purchases of goods and services from Government Accounts........	1,552,000	1,589,000	+37,000
Supplies and materials.............	50,000	50,000	---
Equipment..........................	70,000	72,000	+2,000
Grants, subsidies and contributions....................	40,840,000	42,466,000	+1,626,000
Total budget authority by object......................	46,574,000	48,326,000	+1,752,000

NOTE: Includes FTE's associated with HIV Research Activities. Funds to support these FTE's are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NINR

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	2,019	2,019	2,080	61
11.3	Other than full-time permanent	278	278	281	3
11.5	Other personnel compensation	0	0	0	0
11.8	Special personnel services payments	0	0	0	0
11.9	Subtotal, personnel compensation	2,297	2,297	2,361	64
12.1	Civilian personnel benefits	491	491	506	15
13.0	Benefits for former personnel	0	0	0	0
	Subtotal Pay Costs	2,788	2,788	2,867	79
21.0	Travel and transportation of persons	91	91	76	(15)
22.0	Transportation of things	15	15	15	0
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	90	90	90	0
24.0	Printing and reproduction	70	70	70	0
25.0	Other Services	1,905	1,670	1,712	42
26.0	Supplies and materials	50	50	50	0
	Subtotal non-pay costs	2,221	1,986	2,013	27
	Total Administrative Costs	5,009	4,774	4,880	106

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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National Institutes of Health

National Institute of Nursing Research

Significant Items in the Senate Appropriations Committee Report

Item	Action Taken or To be Taken
1994 Senate Report	
Community-based interventions	
1. The Senate in its report 103-143, page 109, stated: "...The Committee looks forward to findings from NINR-funded health promotion studies such those that examine community-based interventions to reduce the prevalence of cardiovascular risk factors in rural children; develop ways to have a positive effect on decisions regarding alcohol and tobacco use; and encourage good diet and exercise habits in young people.	1. The NINR has undertaken several initiatives to examine community-based interventions focused on health promotion and disease prevention. For example, three exploratory centers have been funded that are examining the factors underlying the initiation and maintenance of health promoting and risk taking behaviors. Pilot studies are focusing on tobacco and alcohol initiation and use, teen pregnancy, diet and exercise interventions, and oral health. Populations are drawn from diverse racial and socioeconomic backgrounds. Additionally, NINR is supporting research to improve health outcomes, e.g., completing immunizations, changing tobacco use, and preventing unwanted teen pregnancy. Strategies include use of adolescent peer educators in community sites and home visits from nurse educators. Future studies will focus on the influence of environmental factors, both social and physical, that predispose young children toward activity and dietary patterns. Additionally, the role of parents and family in the acquisition of health behaviors in young children will be addressed.

Item	Action Taken or To Be Taken
Minority Health	
2. The Senate in its report 103-143, page 109, stated: "... The Committee urges the NINR to continue to address minority health concerns through the development of culturally sensitive nursing interventions. Cross-cutting all NINR programs, research on a range of minority health issues such as prevention of low-birth weight, adolescent health, diabetes, cancer, and long-term care of older persons is focused on the development of a better understanding of social, cultural, and biological variables linked to various disease states and the care of affected individuals.	2. NINR funds several cross-cutting, culturally sensitive research projects aimed at a broad range of minority health issues. Currently funded studies include a racially and culturally sensitive community-based intervention among church-based Southern African-American adults who are at risk for developing colon cancer and an after-school and summer program for African-American rural fifth graders, designed to promote physical fitness and reduce tobacco and alcohol use. Additionally, NINR supports research in the areas of long-term care for older minority persons with chronic illness; racially and culturally sensitive research to improve the health of pregnant minority women and their babies; and research to reduce the rates of morbidity and mortality of low birth weight infants.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amt. Authorized	1994 Appropriation	1995 Amt. Authorized	1995 Budget Request
Research and Investigation..	Section 301	42§281	Indefinite	$42,542,000	Indefinite	$44,181,000
National Institute of Nursing Research..................	Title IV, Part E	42§287	Indefinite		Indefinite	
National Research Service Awards....................	Section 487(d)	42§288	$400,000,000	4,032,000	such sums as necessary	4,145,000
Total Budget Authority...				46,574,000		48,326,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1987	---	$16,700,000	$20,000,000	$20,000,000
1988	16,133,000	24,744,000 2/	23,566,000	23,380,000
1989	24,400,000 3/	27,417,000 4/	28,107,000	29,139,000
1990	29,970,000 5/	32,969,000	34,969,000	33,935,000 6/
1990 Sequester				-422,000
1991	35,127,000	37,289,000 7/	40,013,000	39,722,000 8/
1991 Sequester				-1,000
1992	43,747,000	43,143,000	45,880,000	44,970,000 9/
1993	48,568,000	47,363,000	49,000,000	48,119,000 10/
1994	48,975,000	51,018,000	51,018,000	51,018,000
1995	48,326,000 11/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Does not include funding for AIDS research consolidated at the Secretary's level.

3/ The 1989 request excludes funds for AIDS research and education ($707,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

4/ Excludes $2,690,000 in NRSA training programs not considered.

5/ The 1990 request excludes funds for the National HIV Program ($999,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

6/ Excludes enacted administrative reduction of $34,000.

7/ Excludes $4,233,000 in NRSA training programs not considered.

8/ Excludes enacted administrative reductions of $1,046,000.

9/ Excludes enacted administrative reductions of $226,000.

10/ Excludes enacted administrative reductions of $472,000.

11/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Nursing research....	---	$33,731	---	$37,811	---	$40,476	---	$41,495	---	$43,139	---	+$1,644
Intramural research...	5	150	7	198	9	373	10	471	9	469	-1	-2
Research management and support.........	33	3,466	39	4,206	43	4,662	42	4,608	42	4,718	---	+110
Subtotal, obligations	38	37,347	46	42,215	52	45,511	52	46,574	51	48,326	-1	+1,752
Unobligated balance lapsing...........		17		4		19		---		---		---
Total budget authority.........	38	37,364	46	42,219	52	45,530	52	46,574	51	48,326	-1	+1,752

Justification

National Institute of Nursing Research

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
52	$45,530,000	52	$46,574,000	51	$48,326,000	-1	$1,752,000

General Statement

In this time of National health care reform, the primary mission of the National Institute of Nursing Research (NINR) holds particular significance to the health and well being of the American Public. The development of a scientific base to strengthen the health care that promotes health, prevents disease, and ameliorates the effects of illness and disability, as well as the practice of nursing, will improve the quality of health care provided to the American people and in many instances, may contribute to reducing the cost of the delivery of this care.

The promise of significant future scientific advancement, through the work of the National Institute of Nursing Research, has been augmented by the recent designation to Institute status. Opportunities for collaboration and program development are greatly enhanced by this new status and ensure that all statutory opportunities available to other Institutes and their research constituencies will be available to the NINR and the nursing research community.

The scientific knowledge gained from these programs has enhanced the health care of individuals and their families. Specifically, the creation and demonstration of the effectiveness of a behavioral treatment/intervention to reduce the incidence and severity of nausea and vomiting in patients receiving chemotherapy contributed significantly to the understanding of the complex physiological mechanisms and mitigation of the effects of chemotherapy-induced nausea. The advancement of this scientific knowledge focuses on symptom management of acute and chronic illness, impacts a critical health concern, and offers the promise of the development of future interventions using the baseline knowledge gained from this project.

Other scientific advances impacted on the promotion of health and prevention of disease in low birth weight infants and aging adults. A valid clinical assessment tool to evaluate central nervous system development in low birth weight/preterm infants was developed and tested. This tool allows for the early identification and subsequent intervention of those infants at risk for neurobehavioral sequelae. The aging population benefitted from research that assists in preventing hip fractures. The development and testing of the wearability of passive protective hip joint clothing reduced the rate of hip fracture and increased the rate of adherence in wearing the device among the aging population studied.

Advances aimed at the enhancement of the environment in which nursing care is delivered include the design and testing of special care units (SCU) for patients determined to be chronically critically ill and requiring complex intensive nursing care. Preliminary findings reveal a 10 percent decrease in the mortality rate of the SCU patients over the mortality rates documented in traditional intensive care units (ICU), with a concomitant 12 percent reduction in the rate of sepsis. Total charges were 5 percent less than traditional ICU's for the SCU patients and actual costs were 7 percent less, representing a savings of $1.21 million for the single hospital involved in the study. If replication of this study on a larger scale reveals similar results, a new clinical approach to the care of chronically critically ill patients could be implemented universally that is equally effective and less costly than traditional intensive care.

In FY 1995, the NINR plans to emphasize research in the areas of community-based health care models; health behavior in younger children; and management of symptoms associated with normal processes in mid-life women.

Community-based health care models. The Health Care Reform debate has illuminated the complexities of the delivery of quality, cost-effective health care to vulnerable populations in both urban and rural settings. Clinical management of episodes of care across multiple health care settings, and frequent use of health care during crisis, rather than prevention, make this a compelling health care problem. The NINR will publish a request for applications (RFA) for new initiatives and target research funding for the development and testing of community-based nursing models of health care designed to promote health, prevent disease, provide cost effective quality care and maintain effective clinical management of episodes of care across health care settings.

Health and behavior in younger children. It is apparent from research to date that risk factors for chronic disease develop early in childhood. Little understanding exists about how individuals are shaped by their early childhood environments in ways that prevent or promote the adoption of risk-taking versus health-promoting behaviors. Some data suggest that combining family approaches to disease prevention with individual child-oriented and school-based approaches may be the most effective prevention strategy. Further investigation of family processes as determinants of both prevention and health promotion behaviors in young children from diverse populations is warranted. In FY 1995, NINR will expand this area of research through emphasizing investigations that explain how varying patterns of health behaviors develop in young children and the sequential development of these behaviors over time. These studies will focus on the interaction of the environmental influences, both social and physical, with biological and cognitive characteristics to predispose young children toward activity and dietary patterns; the biological, cognitive and social basis for the development of positive coping patterns in young children of differing ethnic/racial backgrounds; the development of health-enhancing resiliency among young children in adverse circumstances; and the role of parents and family in the acquisition of health behaviors in young children from diverse populations.

Symptoms associated with normal processes in mid-life women. A number of poorly understood and ill-defined symptoms and other syndromes occur in some mid-life women. They include functional disorders, changes in cognition and perception, and memory alteration. Lack of specific pathology often leads to labeling these syndromes as functional or psychosomatic and lead to treatment with nonspecific pharmacologic agents or surgery. The accompanying pattern of side effects from these treatments sometimes further debilitates the patient. Building on prior programs describing these symptoms, NINR will expand this area of research through the issuance of a program announcement on mid-life women, calling for research to better understand the relationship between menopause symptoms and the biobehavioral mechanisms responsible for their alleviation or exacerbation and the testing of alternative interventions.

The President's appropriation request of $48,326,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Institute of Nursing Research during the last 5 years has been as follows:

Year	Amount	FTE
FY 1990	$32,526,000	29
FY 1991	37,364,000	39
FY 1992	42,219,000	48
FY 1993	45,530,000	52
FY 1994	46,574,000	52

Purpose and Method of Operations

The budget of the National Institute of Nursing Research is comprised of three distinct budget activities. The Nursing Research budget activity supports extramural research and training, and is comprised of three major program areas: Acute and Chronic Illness, Health Promotion/Disease Prevention, and Nursing Systems. Funding mechanisms used to support these program areas include research project grants, research centers, other research grants, research training, and research and development contracts.

The second budget activity is the Intramural Research Program. This program develops and conducts clinical research programs for the health care of individuals and nursing practice; provides training for nurse scientists; and disseminates research findings. Two laboratories comprise the Division of Intramural Research, NINR: the Clinical Therapeutics Laboratory (CTL) and the Laboratory for the Study of Human Responses to Health and Illness (HRHI).

The third and final budget activity, Research Management and Support, provides for the administrative management and scientific direction of the Center.

Overall Budget Policy

The FY 1995 budget request for the NINR totals $48,326,000. This amount represents a total increase of $1,752,000 or 3.8 percent over FY 1994. The FY 1995 budget request for research project grants is $34,116,000. This level will support a total of 141 research project grants: 98 noncompeting research project grants, a decrease of 15 awards from FY 1994; and 43 competing research project grants, an increase of 15 awards over FY 1994. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a four percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring costs such as equipment. Within the competing component, average grant awards received an increase approximately equal to the biomedical research and development price index.

In research centers, the request provides $1,873,000 to continue funding seven centers, this is a $74,000 increase over FY 1994.

The FY 1995 request maintains the same number of awards in the other research mechanism as in FY 1994. This allows continued funding for research career awards, research demonstration projects, small instrumentation grants, and a new small-grant initiative in community-based models of nursing care.

In research training, the amount provided is $4,145,000 which will allow funding for 203 full-time training positions, the same number funded in FY 1994.

The amount requested for research and development contracts is $673,000, approximately the same level as FY 1994.

The FY 1995 request provides $469,000 for intramural research, a decrease of $2,000 from FY 1994.

In research management and support, the FY 1994 request provides $4,718,000, an increase of $110,000 over FY 1994. This amount will cover a portion of the increases for centrally furnished services, pay-related costs, and other supplies, equipment, and services. An administrative reduction of $66,000 is also reflected.

National Institute of Nursing Research

Extramural Research

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act. 1995 Authorization: Pending

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$40,476,000	$41,495,000	$43,139,000	+$1,644,000

The Nursing Research budget activity supports extramural research and research training awards in the three major program areas of Health Promotion/Disease Prevention, and Acute and Chronic Illness, and Nursing Systems.

Health promotion research is aimed at the development of strategies and interventions to promote wellness and decrease the vulnerability of individuals and families to illness and disability across the human lifespan, from infants to older adults.

Research of acute and chronic illness is focused on human responses to acute and chronic illness and disability. This research is also aimed at the biological and behavioral factors that contribute to these conditions, as well as on ways to mitigate the effects of the illness/disability.

The research of the Nursing Systems program concentrates on the delivery of health care and its influence on patients, as well as the environmental influences affecting the delivery of nursing care.

Funding for the Nursing Research activity during the last 5 years has been as follows:

Year	Amount
FY 1990	$29,534,000
FY 1991	33,731,000
FY 1992	37,811,000
FY 1993	40,476,000
FY 1994	41,495,000

Rationale for the Budget Request

The FY 1995 budget request for the Nursing Research budget activity is $43,139,000 an increase of $1,644,000 over the FY 1994 estimate of $41,495,000. Developed on the scientific bases of current research in their respective programs, the following are samples of research activities that will be supported through this activity.

Health and Behavior Research

Health behaviors of individuals, families, and groups are inextricably related to the delivery of health care. A majority of NINR funding is directed toward behavioral, physiological, and environmental factors that prevent disease and promote health across the life span in vulnerable populations.

NINR research in FY 1995 will focus on the identification, development, implementation, and evaluation of effective, culturally sensitive, approaches to establishing health promoting behaviors and changing health compromising behaviors. Particular emphasis will be placed on how patterns of health behaviors develop in young children and the sequential development of these behaviors over time. Specifically, this research includes investigations such as a longitudinal study of biobehavioral cardiovascular risk factors in 120 sets of twin children, ages 6-11, and their parents. Additionally, NINR supports a descriptive study among 4th, 5th, and 6th graders designed to describe the direct and total effects of self-esteem, health knowledge, motivation, health status, obesity, blood pressure, family environment and parental health motivation on exercise, dietary intake and tobacco use.

Studies supported currently include an investigation that focuses on the sexual risk behaviors of college-aged adolescents, comparing the intrapersonal factors and social norms of freshman and sophomore men and women relative to alcohol, drug, and condom use; a specialized Center for Women's Health Research that focuses on mid-life health issues including: the health and health seeking behaviors of a diverse cohort of mid-life women, and specific physical symptoms and stress responsivity; as well as a test of a nursing intervention designed to increase the frequency and proficiency of breast self-examination.

Prevention Research

Prevention research addresses the complex biomedical and social processes believed to influence the incidence and prevalence of illness. As the cost of health care continues to rise, prevention must be our national objective. The Health Promotion and Disease Prevention Program of the NINR focuses on the behavioral, physiological, and environmental factors that prevent disease and promote health across the entire span of human life.

Investigations of particular interest include projects focused on the prevention of low birth weight; identification of risk factors and promotion of healthy behaviors in children and adolescents; and women's health. Currently supported projects include a collaboration with the National Institute of Child Health and Human Development, the Office of Research on Minority Health, and the District of Columbia to develop scientifically based intervention programs aimed at reducing the infant morbidity and mortality rates in the District of Columbia. These interventions will encompass the reproductive life-span from the pre-conceptual to the postpartum period. Additionally, three exploratory centers, supported by the NINR, focus on the factors underlying the initiation and maintenance of health promoting and risk taking behaviors such as tobacco and alcohol use, teen pregnancy, diet and exercise interventions, and oral health. Populations are drawn from diverse racial and socioeconomic backgrounds. NINR also supports research in the areas of prenatal care and health in pregnancy; screening and early detection as deterrents to chronic illness; tuberculosis education and treatment adherence; and alternative models of nursing care delivery.

Minority Health

Nursing is committed to supporting scientific research on a broad range of minority health issues. Investigations supported by the NINR cut across all NINR research programs and are aimed at the health care needs of minority populations at risk for illness and disability.

Currently funded research projects include a community-based nursing intervention among church-based Southern African-American adults who are at risk for developing colon cancer. This intervention uses a church-based advisory group and culturally/racially matched data collectors to implement an adherence promotion strategy for ingestion of increased dietary fiber. An after school and summer physical activity promotion program for fifth graders living in a rural, predominantly African-American community in South Carolina is designed to promote physical fitness, and reduce tobacco and alcohol use, with older adolescents trained to serve as program leaders. Additionally, NINR supports research in the areas of long-term care for older minority persons with chronic illness; racially and culturally sensitive research to improve the health of pregnant minority women and their babies; and research to reduce the rates of morbidity and mortality of low birth weight infants.

Patient Outcomes Research: Examining Nursing Effectiveness

In the current health care environment information on improving quality of care, identifying levels and appropriateness of nursing interventions, and distinguishing the nursing contribution to a clinical outcome in a multidisciplinary context of care delivery, is critical to understanding and examining the effectiveness of care provided to patients, families and population groups.

NINR published a request for application (RFA) on studies of clinical outcomes and nursing practice. The resultant studies examined the impact of the clinical course of cancer and its treatment upon older patient's needs for assistance, the involvement of their families, and the costs of providing this care in the context of a community-based model of home care; tested the outcomes of a community-based nursing intervention among African-American adults who are at risk for developing colon-cancer; and examined selected methods of analysis which can facilitate measuring change in quality of life as a clinical outcome, focusing on individual patterns of change in a group of patients undergoing radiation therapy for cancers of the head and neck. NINR will expand the outcomes research program by instituting a small grants program that will include a focus on cost effectiveness and clinical effectiveness of nursing interventions. This will continue the emphasis on methodological issues and the development of valid, reliable, sensitive and specific measures of outcome effectiveness.

Women's Health

There is a critical need for more information regarding the impact of women's changing roles and life experiences on their health. Nursing research provides a unique contribution to the study of the broader context of women's lives by examining both their psychosocial and physiological well-being, along with the social, cultural, and environmental influences on their health.

Breast cancer is a critical health problem. NINR supports studies to improve women's knowledge and behavior concerning breast cancer prevention and detection, as well as research that leads to effective nursing interventions to support and enhance treatment of women with breast cancer. For example, one investigation has focused on breast self-examination behavior to identify interventions that will increase the frequency of this important behavior. Preliminary findings suggest that the group of patients that received the intervention increased breast screening behaviors, as well as improved their proficiency in conducting the examinations. Most encouraging is the fact that this group has significantly improved in actual lump detection. If this intervention is implemented on a larger scale clinical basis, it could significantly impact the early diagnosis and treatment of life threatening breast malignancies. Additional research concentrates on further quality of life issues of breast cancer patients and their caregivers. Symptoms of distress, depression, diminished mental health status, alterations in sleep patterns, as well as caregiver depression and feelings of responsibility are being addressed.

NINR supported research examines factors basic to women's health and development across the lifespan. Investigations on such topics as nutrition, exercise, childbearing, menstruation and menopause, coping with chronic illness and other aspects of self regulation and caregiving are being conducted. Other research projects are addressing stress and adaptation to life transitions, such as parenthood, retirement, and widowhood. Further information is needed on gender differences, gender-specific behaviors, the biobehaviorial interface between these factors, and how they serve to prevent, stimulate, or reduce the risk for and/or progression of diseases that are the leading causes of death in women.

Low Birth Weight: Prevention and Improved Care

Babies, a treasured resource in this country are dying at an unacceptably high rate. Great strides have been made in describing overall risk factors for low birth weight contrasting African-Americans and Caucasians. However, rates of low birth weight among African-Americans remain unchanged. Further studies are required to address causal pathways and what can be done to modify their outcomes through changes in behaviors and lifestyles.

NINR is supporting culturally sensitive low birth weight research in vulnerable populations as demonstrated in the following examples: a study evaluating the effectiveness of prenatal and postpartum nurse home visitations as a means of enhancing the health and well-being of socially disadvantaged women and their first-born child; an intervention study testing the effectiveness of intensive prenatal telephone contacts by clinical nurse specialists on birth outcomes of a sample of low income African-American women; and a study investigating the cost benefit of substituting half of all routine prenatal clinic visits with nurse home visits and telephone contact for a population of high-risk women.

Alzheimer's Disease Symptom Management Research

The impact of Alzheimer's disease or related dementias (ADRD) on patients, families, and society is severe; in 1991, estimates show that the total costs for dementia in the U.S. exceeded $113 billion. It is estimated that over 6 million individuals will have ADRD by the year 2040--a 50 percent increase over the 4 million people currently experiencing these conditions. It is critical that interventions be developed that reduce the patient's secondary symptoms and preserve optimal functioning, given that it is not yet possible to prevent, adequately treat, or alter the course of the conditions.

Preliminary investigations into symptoms such as wandering, disturbed sleep, and agitation, have served to establish a strong scientific base for large-scale clinical trials which address behavioral, environmental, social, and organizational interventions to deal with ADRD symptoms. Interventions being tested include reducing the use of psychotropic medications in nursing home ADRD patients and providing environmental cues; decreasing sleep disruption in ADRD patients and their caregivers; and investigating the effects of a walking and conversational treatment on the communication ability of ADRD patients. Further investigation is required on a larger scale clinical basis to develop refined innovative approaches to the management of ADRD symptoms.

Symptom Management of Acute Pain

Pain is a costly, critical health concern that causes suffering, but may adversely affect immune function and may even be related to increased tumor growth. The cost for individuals and society reach beyond economic factors and extend into their quality of life. In the hospitalized patient, pain may be associated with increased length of stay, longer recovery time, and poorer patient outcomes, all of which have health care quality and cost implications.

Nursing contributes to the research efforts on pain through the development of improved assessment measures and biobehavioral interventions to assist patients in dealing with this distressing syndrome. Examples of such interventions are evidenced through examination of methods to assess pain in infants; investigation of methods to assess and manage pain in adolescents and children; and the testing of two protocols to treat pain in children of different ethnic backgrounds, ages 3-7, with a particular focus on culturally-sensitive assessment tools. NINR is particularly interested in stimulating research that will propose innovative interventions dealing with both pharmacological regimens and nonpharmacological techniques.

Tuberculosis: Adherence Intervention Research

The rapid rise of tuberculosis over the past four years has placed an enormous burden on the health care system. Resistant disease strains create an additional level of complexity to caring for those vulnerable to infection.

Nurses play a critical role in increasing adherence and compliance to treatment.

NINR issued a request for applications to address the problems of adherence with tuberculosis treatment. Resultant projects being supported include one to test the effectiveness of an educational intervention which uses video-taped examples of desired health and treatment behaviors portrayed by actors with whom the targeted patients will identify. This study will use adherence techniques adapted to the various target audiences. Large minority subgroups will be included to assist in the identification of differences among different segments of the population most affected by this disease and assist in the selection of the most effective, culturally sensitive educational tools. A second project involves collaboration among county health department nurses and university scientists to examine the components of a program of directly observed prophylactic therapy for homeless persons infected with the tubercle bacillus, but without evidence of active disease. This study will also examine the cost-effectiveness of the intervention and the effectiveness of multiple options for the selection of a site for therapy, the personnel best suited for follow-up, and the method used for follow-up care. NINR will continue to contribute to intra- and inter-agency coordination of research efforts through participation in the Tuberculosis Initiative Subcommittee of the NIH Health and Behavior Coordinating Committee.

Optimizing Health of Older Adults

Improving the health and quality of life of older adults is a major goal in the Healthy People 2000 Objectives. The probability that the aging individual will be able to maintain functional autonomy, an independent lifestyle, and assert control over their lives, is enhanced through promoting healthy self care. With this in mind, the objective is to intervene while the individual is in relatively good health, i.e., to maintain that state of health as long as possible, rather than wait until illness or disease occurs.

NINR continues to support a full array of health promotion studies with older adults. Investigations include studies examining the effects of increasing physical functional capacities and reducing injuries by improving mobility, strength, and balance; development and testing of a hip joint protective device to determine its effect on the rate of hip fracture and adherence in wearing the device; as well as the testing and development of several community-based nursing intervention models designed to manage commonly experienced symptoms, prevent the onset of further disabilities, and facilitate the transition between health care settings and home. Additionally, the NINR supports investigations that are aimed at the development of interventions to enhance the quality of care and life of nursing home residents by increasing independence and self management among residents, maintenance of family participation in care, and the encouragement to discharge to home whenever possible.

National Institute of Nursing Research

Intramural Research Program

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act. 1995 Authorization: Pending

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
9	$392,000	10	$471,000	9	$469,000	-1	+$2,000

The Division of Intramural Research is comprised of two distinct laboratories, the Clinical Therapeutics Laboratory (CTL) and the Laboratory for the Study of Human Responses to Health and Illness. The CTL conducts a program of research that studies the biophysiologic and behavioral basis for and the effectiveness of interventions for nursing practice and health care. CTL projects focus on prevention and treatment of symptoms or side effects that occur as a result of diseases, such as HIV infection; injuries, and other health conditions, such as aging; or their treatment. Other studies examine compliance with prevention, diagnostic, or treatment measures.

The HRHI conducts a program of research that focuses on the biophysiologic and behavioral aspects of human responses that occur in health and illness including processes, mechanisms, and environments that influence health, health promoting, and health maintaining behaviors; interventions that reduce the risk of illness; and interventions that facilitate adaptation to illness or disability.

Funding for the Intramural Research activity during the last 5 years has been as follows:

Year	Amount	FTE
FY 1990	$191,000	2
FY 1991	150,000	5
FY 1992	198,000	7
FY 1993	392,000	9
FY 1994	471,000	10

Rationale for the Budget Request

The FY 1995 request for intramural research is $469,000, a decrease of $2,000 from FY 1994. The following are examples of current and planned program activities within the Intramural Research Program.

The CTL staff has developed a Symptom Management in Aging Initiative that encompasses the prevention, detection, assessment, and treatment of symptoms and conditions prevalent in older Americans. In collaboration with other investigators, including those of the National Institute of Aging, the CTL is studying urinary incontinence in older adults and is investigating the effectiveness of clinical therapeutics for incontinence. Because of the prevalence of incontinence and costs associated with its management, a study is focusing on the natural development of incontinence in dependent elderly in the long-term care setting and on the effectiveness of a behavioral intervention in reducing incontinence. A second study is investigating the combined effects of estrogen therapy and pelvic muscle exercise in the treatment of incontinence and the distressing urinary symptoms of urgency and frequency in community-dwelling post menopausal women. A third study will focus on providing an intervention to post hip fracture patients in the acute care setting to prevent incontinence and reduce post operative urinary complications, such as urinary tract infections and incomplete bladder emptying, and to reduce the risk of institutionalization of the older adult. Future studies will focus on the prevention of incontinence in post menopausal women and other populations.

The Laboratory for the Study of Human Responses to Health and Illness (HRHI) staff has developed a program of research that is aimed at investigations to improve the quality of life for individuals and families engaged in health promoting/risk reducing behaviors and/or living with a chronic illness, as well as interventions that facilitate adaptation in illness or disability. Studies currently in progress include a study, in collaboration with the National Heart, Lung, and Blood Institute and the National Institute on Aging, of caregiving and quality of life in women who care for aging men with dementia. NINR is focused on studying the effects of dementia on the caregiver burdens and quality of life of family members. The study will be expanded to study the effects of caregiver burden on immunocompetence, as well as to explore factors that facilitate successful coping following the death of a loved one with dementia.

Another study focuses on the role of functional status in persons with chronic illnesses. The second phase of this study will conduct physiologic testing to correlate objective measurements of functional status to subjective measures. This will enable investigators to more accurately evaluate functional status as a patient outcome of chronic illness and ultimately, develop interventions aimed at improving the quality of life for individuals experiencing an acute or chronic illness. Future studies will also focus on improving the quality of life of aging women.

National Institute of Nursing Research

Research Management and Support

Authorizing Legislation - Sections 301 and 487(d) of the Public Health Service Act. 1995 Authorization: Pending

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
43	$4,662,000	42	$4,608,000	42	$4,718,000	--	+$110,000

The Research Management and Support (RMS) activity provides administrative support and scientific management for the grants and contracts awarded under the Nursing Research activity, as well as for overall program direction and policy development. Associated with this activity is the immediate Office of the Director and the Institute's extramural scientific and administrative staff.

Rationale for the Budget Request

The FY 1995 request for Research Management and Support (RMS) is $4,718,000, an increase of $110,000 above the FY 1994 estimate of $4,608,000. This amount will cover a portion of the increases for centrally furnished services, pay-related costs, and other supplies, equipment, and services. An administrative reduction of $66,000 is also reflected.

Funding for the Research Management and Support activity during the last 5 years has been as follows:

Year	Amount	FTE
FY 1990	$2,801,000	27
FY 1991	3,483,000	34
FY 1992	4,210,000	41
FY 1993	4,662,000	43
FY 1994	4,608,000	42

This activity will continue to provide the program guidance, planning and evaluation, leadership, and overall administration for the programs and information directed toward scientists, practicing nurses, and the public.

Direct support is also provided for the operation of the NIH Nursing Research Task Force and the continuing development and coordination of the National Nursing Research Agenda.

NATIONAL INSTITUTES OF HEALTH

National Institute of Nursing Research

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director........	3	3	3
Office of Scientific Review...	6	6	6
Office of Planning, Analysis and Evaluation.............	5	5	5
Office of Information and Legislative Analysis........	4	4	4
Office of Administrative Management.................	12	11	11
Division of Extramural Research...................	13	13	13
Division of Intramural Research...................	9	10	9
Total, NINR	52	52	51

NOTE: Includes FTE's associated with HIV Research Activities. Funds to support these FTE's are included in the NIH Office of AIDS Research.

Average GS/GM Grade

1990........................	12.4
1991........................	10.6
1992........................	10.7
1993........................	11.1
1994........................	11.7
1995........................	11.7

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FISCAL YEAR 1995

Volume VII

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
National Center for Human Genome Research
Fogarty International Center
National Library of Medicine
Buildings and Facilities
Office of the Director
Office of AIDS Research

Justification of
Estimates for
Appropriations Committees

79–986 2957

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

	FY 1995 Estimate		Page
	FTEs	Amount	Number
National Center for Human Genome Research	183	$152,010,000	1
John E. Fogarty International Center for Advanced Study in the Health Sciences	78	13,745,000	33
National Library of Medicine	599	135,330,000	61
Buildings and Facilities	---	113,539,000	97
Office of the Director	704	233,522,000	113
Office of AIDS Research	---	1,379,052,000	153

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

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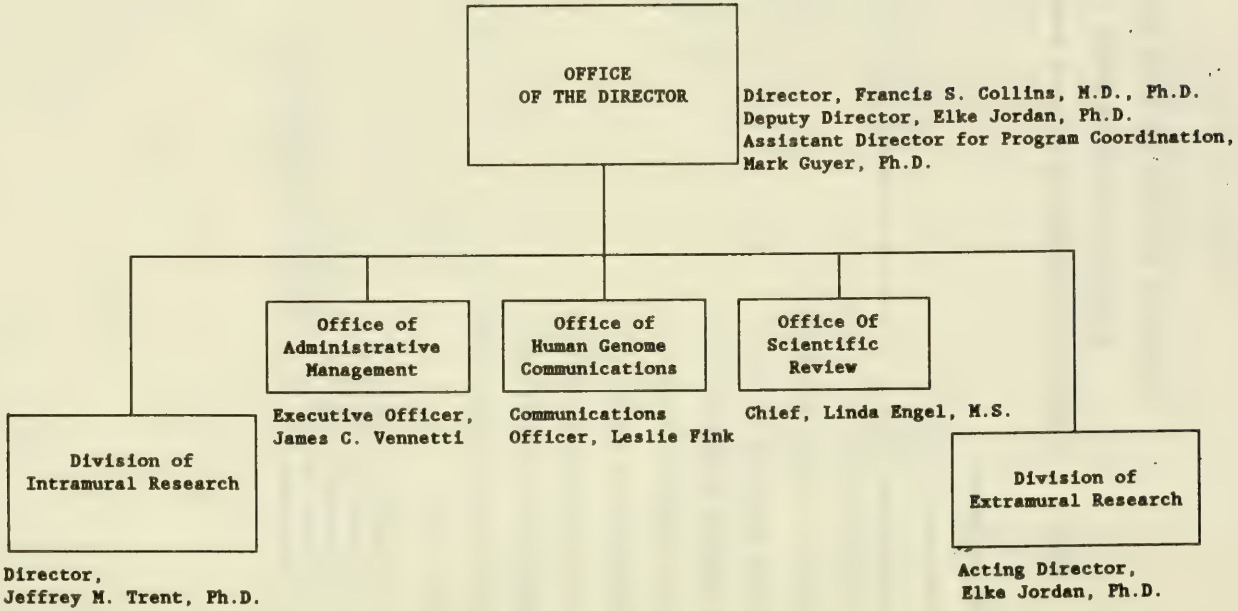
NATIONAL CENTER FOR HUMAN GENOME RESEARCH

Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

For carrying out section 301 and Title IV of the Public Health Service Act with respect to human genome research, [$128,701,000] *$152,010,000 of which $1,591,000 shall not become available for obligation until September 19, 1995. (Department of Health and Human Services Appropriation Act, 1994.)*

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National Center for Human Genome Research

Language Analysis

Language Provisions	Explanation
"...of which $1,591,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Center For Human Genome Research

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation......................	$107,217,000	$128,701,000	$152,010,000
Section 511 0.8 percent reduction...	-858,000	---	---
Section 513 cons. svs reduction.....	-28,000	---	---
Section 216 S & E reduction.........	-92,000	---	---
Subtotal, adjusted appropriation..............	106,239,000	128,701,000	152,010,000
Real transfer to: other account for Tuberculosis....	-105,000	---	---
Subtotal, adjusted budget authority............	106,134,000	128,701,000	152,010,000
Unobligated balance lapsing.........	-39,000	---	---
Total obligations......	106,095,000	128,701,000	152,010,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1993 - $7,085,000; FY 1994 - $1,750,000; FY 1995 - $2,200,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	105	$33,556,000	78	$41,996,000	74	$44,402,000
Admin. supplements	(10)	1,361,000	(4)	449,000	(4)	467,000
Competing:						
Renewal	19	8,748,000	15	5,083,000	22	9,893,000
New	30	16,356,000	22	9,503,000	15	5,292,000
Supplements	1	78,000	0	0	0	0
Subtotal, competing	50	25,182,000	37	14,586,000	37	15,185,000
Subtotal, res. proj	155	60,099,000	115	57,031,000	111	60,054,000
Research centers:						
Specialized/comp. centers	13	31,427,000	13	32,624,000	14	35,195,000
RCMI	(2)	250,000	(2)	269,000	(2)	280,000
Subtotal, centers	13	31,677,000	13	32,893,000	14	35,475,000
Other research:						
Research career programs	12	856,000	12	883,000	12	908,000
Other research related	41	3,410,000	46	4,288,000	46	4,408,000
Subtotal, other research	53	4,266,000	58	5,171,000	58	5,316,000
Total, research grants	221	96,042,000	186	95,095,000	183	100,845,000

Training:						
Individual awards:						
Noncompeting	16	445,000	20	543,000	13	369,000
Admin. supplements	(1)	1,000				
Competeting	8	197,000	1	34,000	4	114,000
Subtotal, individual	24	643,000	21	577,000	17	483,000
Institutional awards:						
Noncompeting	146	3,315,000	147	3,532,000	13	390,000
Competing					93	2,236,000
Subtotal, institutional	146	3,315,000	147	3,532,000	106	2,626,000
Total, training	170	3,958,000	168	4,109,000	123	3,109,000
Research and development contracts	5	517,000	7	2,266,000	7	2,330,000
	FTEs		FTEs		FTEs	
Intramural	3		92	21,000,000	122	39,387,000
Research management and support	52	5,617,000	61	6,231,000	61	6,339,000
Total	55	106,134,000	153	128,701,000	183	152,010,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Summary of Changes

1994 Estimated budget authority	$128,701,000
1995 Estimated budget authority	152,010,000
Net Change	+23,309,000

	1994 Current Estimate Base		Change from Base	
	FTE's	Budget Authority	FTE's	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Research				
a. Within grade increase		$7,207,000		+$85,000
b. Annualization of January 1994 locality pay increase		7,207,000		+76,000
c. One less day of pay		7,207,000		-28,000
d. January 1995 pay increase		7,207,000		+88,000
e. Increased cost of centrally furnished services		1,026,000		+42,000
f. Increase cost of service and supply fund		964,000		+27,000
g. Increase cost of supplies and materials		11,803,000		+330,000
Subtotal				+620,000
2. Research Management and Support				
a. Within grade increase		$3,639,000		+52,000
b. Annualization of January 1994 locality pay increase		3,639,000		+38,000
c. One less day of pay		3,639,000		-14,000
d. January 1995 pay increase		3,639,000		+45,000
e. Increase in FECF unemployment compensation		3,639,000		+2,000
f. Increased cost of centrally furnished services		990,000		+41,000
g. Increase cost of service and supply fund		179,000		+11,000
h. Increase cost of supplies and materials		1,423,000		+39,000
i. Increase cost for FTS				+1,000
Subtotal				+215,000

Summary of Changes (con't)

B. **Program:**	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting.............	78	$41,996,000	-4	+2,406,000
b. Admin supplements........	(4)	449,000		+18,000
c. Competing................	37	14,586,000		+599,000
Total....................	115	57,031,000	-4	+3,023,000
2. Research centers............	13	32,893,000	1	+2,582,000
3. Other research..............	58	5,171,000		+145,000
4. Research training...........	168	4,109,000	-45	-1,000,000
5. Research & dev contracts.....	7	2,266,000		+64,000
	FTE's	Amount	FTE's	Amount
6. Intramural:				
a. Program increase........	92	21,000,000	30	+18,125,000
b. Administrative cost reduction.............	92	21,000,000		-358,000
7. Research management and support:				
a. Administrative cost reduction.............	61	6,231,000		-107,000
Subtotal.....................				+22,474,000
Total changes................				+23,309,000

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.......	153	183	+30
Full-time equivalent of overtime and holiday hours.....................	4	4	0
Average ES salary.......................	$113,600	$116,880	+$3,280
Average GM\GS grade.....................	10.1	10.0	-0.1
Average GM\GS salary....................	43,876	44,863	+987
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)...	57,193	58,484	+1,291
Average salary of ungraded positions....	30,600	31,090	+490
Personnel compensation:			
Full-time permanent..................	5,317,000	7,047,000	+1,730,000
Other than full-time permanent........	2,278,000	3,510,000	+1,232,000
Other personnel compensation..........	397,000	583,000	+186,000
Special personnel service payments....	1,190,000	4,000,000	+2,810,000
Subtotal, personnel compensation......	9,182,000	15,140,000	+5,958,000
Personnel benefits.....................	1,662,000	2,286,000	+624,000
Benefits for former personnel...........	2,000	4,000	+2,000
Travel and transportation of persons....	385,000	701,000	+316,000
Transportation of things................	320,000	384,000	+64,000
Rent, communications, and utilities.....	152,000	154,000	+2,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Printing and reproduction..............	59,000	100,000	+41,000
Other services:			
Consulting services..................	557,000	584,000	+27,000
Other services.......................	5,594,000	8,046,000	+2,452,000
Purchases from government accounts....	4,805,000	6,714,000	+1,909,000
R&D contracts........................	2,266,000	2,330,000	+64,000
Supplies and materials..................	2,431,000	8,154,000	+5,723,000
Equipment...............................	2,082,000	3,459,000	+1,377,000
Grants, subsidies & contributions.......	99,204,000	103,954,000	+4,750,000
Total................................	128,701,000	152,010,000	+23,309,000

National Institutes of Health
Administrative Costs
Budget Authority
NCHGR

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	5,317	5,317	7,047	1,730
11.3	Other than full-time permanent	2,278	2,278	3,510	1,232
11.5	Other personnel compensation	397	397	583	186
11.8	Special personnel services payments	1,190	1,190	4,000	2,810
11.9	Subtotal, personnel compensation	9,182	9,182	15,140	5,958
12.1	Civilian personnel benefits	1,662	1,662	2,286	624
13.0	Benefits for former personnel	2	2	4	2
	Subtotal Pay Costs	10,846	10,846	17,430	6,584
21.0	Travel and transportation of persons	385	385	701	316
22.0	Transportation of things	50	320	384	64
23.2	Rental payments to others	10	0	0	0
23.3	Communications, utilities, and miscellaneous charges	142	152	154	2
24.0	Printing and reproduction	54	59	100	41
25.0	Other Services	13,212	10,363	14,751	4,388
26.0	Supplies and materials	2,850	2,431	8,154	5,723
	Subtotal non-pay costs	16,703	13,710	24,244	10,534
	Total Administrative Costs	27,549	24,556	41,674	17,118

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation......	Section 301	42§241	Indefinite	$124,592,000	Indefinite	$148,901,000
National Research Service Awards	Section 487(d)	42§288	$400,000,000	4,109,000	Such sums as necessary	3,109,000
Total Budget Authority........				128,701,000		152,010,000

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NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1990	$100,000,000	$62,000,000	---[1]	$59,938,000
1990 Sequester				-400,000
1991	108,029,000	66,131,000	108,264,000	87,418,000[2]
1991 Sequester				-1,000
1992	110,487,000	93,115,000	109,309,000	104,762,000[3]
1993	110,429,000	107,217,000	107,217,000	106,239,000[4]
1994	134,549,000	119,030,000	131,925,000	128,701,000
1995	152,010,000			

[1] The Senate did not provide funds for the National Center for Human Genome Research; however, the Senate allowance included $61,847,000 for the Human Genome Initiative within the National Institute of General Medical Sciences' account.

[2] Excludes enacted administrative reductions of $2,313,000 and the enacted rescission of $116,000.

[3] Excludes enacted administrative reductions of $383,000.

[4] Excludes enacted administrative reductions of $978,000.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Budget Authority by Activity
(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
Human Genome Research..		83,681		99,836		100,517		101,470		106,284		+4,814
Intramural Research......							92	21,000	122	39,387	+30	+18,387
Research mangement and support............	37	3,708	44	4,920	55	5,578	61	6,231	61	6,339	0	+108
Total obligations......	37	87,389	44	104,756	55	106,095	153	128,701	183	152,010	+30	+23,309
Unobligated balance lapsing................		9		6		39						
Total, budget authority..	37	87,398	44	104,762	55	106,134	153	128,701	183	152,010	+30	+23,309

Justification

National Center for Human Genome Research

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
55	$106,134,000	153	$128,701,000	183	$152,010,000	+30	+$23,309,000

General Statement

Few research programs have contributed as much to biomedical science in such a short time as has the Human Genome Project. In fiscal year 1994, the number of genes isolated using genome technologies and resources nearly quadrupled over the year before. Continued improvements in gene mapping technologies are likely to spur even greater increases in the rate of gene discovery in fiscal year 1995 and beyond.

Innovations in DNA mapping technologies as well as increased efficiencies and economies of scale have enabled individual laboratories to expand the target of mapping studies from individual chromosomes to the entire genome. Efforts are now underway to place high-quality markers throughout the human genome, such that any gene in the genome is likely to be within 100,000 base pairs of a marker. The quality of these markers, as well as their spacing in the genome, will make it possible for biomedical scientists to find and isolate any gene of interest in a much shorter period of time than previously possible.

An excellent example of the speed with which disease genes can now be isolated using genomic technologies is the recent isolation of a gene for colon cancer by a group of collaborating scientists, including members of NCHGR's new Division of Intramural Research. This gene was isolated within 6 months from the time at which it was located on chromosome 2; such work would have taken several years in the past. Hereditary colon cancer is a common disorder that affects 1 in 200 people in the western world. Causing as many as 1 in 6 cases of colon cancer, as well as an increased risk for uterine cancer, this gene is responsible for the most common of the known inherited susceptibilities to a disease.

The progress in genome science since the Human Genome Project's beginning have led the U.S. funding agencies to review and extend the first set of 5 year goals, established in fiscal year 1991. On the Human Genome Project's third anniversary, a new set of goals covering years 4 through 8 were published. These incorporate the new technological developments into the research plan, keeping it ambitious and on the cutting edge. In addition to refining the current maps, the new plan includes a specific focus on developing new ways to identify genes. Identifying and localizing large numbers of genes will give scientists a ready supply of candidate genes located in regions of interest to them as they search for specific disease genes.

With achievements in mapping leading the successes of the Human Genome Project, increased emphasis must now be placed on the development of DNA sequencing technologies. In many cases, new mapping technologies will make finding a gene the "easy" part. However, in spite of recent improvements, sequencing the DNA to understand the detailed structure of the genes, as well as the control regions that determine how the genes are expressed, is still a relatively slow and cumbersome process compared to what is theoretically possible. Methods that are faster, cheaper, and highly automated are needed. To achieve this, a much larger investment in sequencing technology development is needed.

The rapid pace at which disease genes are being discovered also makes consideration of the social impact of these discoveries paramount. NCHGR's Ethical, Legal, and Social Implications (ELSI) Branch has sponsored a number of important studies to help smooth out the complex interface between genetic technologies and society. Under the ELSI rubric, seminal reports outlining policy options on the use of genetic information in health insurance and on genetic testing in medical practice have been produced. Future projects include studies to examine issues related to genetic testing for predisposition to common illnesses, such as cancer.

As genetic technologies make their way into mainstream medicine at an ever increasing pace, the importance of public understanding of these technologies becomes critical. In this new age of "molecular medicine," many Americans lack the necessary understanding of DNA, genes, mutations, and inheritance to make informed decisions with their doctors about their health care. To ensure that citizens gain the most benefit from the new technologies spinning off from the Human Genome Project, NCHGR will be increasing its educational efforts to prepare the public to make informed decisions.

The President's appropriation request of $152,010,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Center for Human Genome Research for the past 5 years has been as follows:

	Amount	FTE
FY 1990	$ 59,538,000	26
FY 1991	87,398,000	37
FY 1992	104,762,000	44
FY 1993	106,134,000	55
FY 1994	128,701,000	153

Additionally, in FY 1993 about $7,000,000 was provided to the NCHGR from the NIH Director's Discretionary Fund for initiating the new Division of Intramural Research. With the dramatic achievements in the Human Genome Projects's mapping effort, the translation of this knowledge to identification of disease genes and ultimately cures for genetic diseases has become the focus for medical genetics. The "start-up" funds for the NCHGR intramural program in FY 1993 launched a major initiative at the NIH in this area. A critical mass of scientists has been recruited to take basic research findings from bench to bedside.

Purpose and Method of Operation

The NCHGR carries out its mission through the support of research project grants, research center grants, research career awards, other research grants, training grants and fellowships, and inter-agency agreements with other Federal agencies. In addition, the NCHGR supports the new Division of Intramural Research which conducts research on genes and their function in the causation of disease and hopefully the eventual cure of human diseases. The scientific and administrative management and other overhead items are funded through the research management and support budget mechanism.

Overall Budget Policy

The FY 1995 budget request for the National Center for Human Genome Research is $152,010,000. This amount represents an increase of $23,309,000 or 18.11 percent over the FY 1994 estimate. This budget was developed in accordance with the principles of the NIH Cost Management Plan. Within the noncompeting component, average grant awards received a 4 percent increase over the direct cost level of the FY 1994 amount unless exceptions were made for specific justified program requirements and one time non-recurring cost such as equipment.

The FY 1995 budget request for research project grants is $60,054,000, 5.3 percent over FY 1994. This level will support 111 as compared to 115 in FY 1994. NCHGR will support 74 noncompeting research project grants at $44,402,000 and 37 competing research project grants compared to 78 and 37, respectively in FY 1994. The average cost of competing grants will increase by the Biomedical Research Development Price Index of 4.1 percent in FY 1995. The FY 1995 budget request for research centers is $35,475,000, a 7.8 percent increase over FY 1994. NCHGR expects much of the massive amount of genome-wide mapping and sequencing to be conducted by the Genome Science and Technology Centers (GESTEC), of which most are research centers.

The FY 1995 budget requests $5,316,000 for other research grants and $2,330,000 for research and development contracts and inter-agency agreements, a 2.8 percent increase over the FY 1994 estimate for the same number of awards.

The FY 1995 budget requests $3,109,000 for research training awards, a decrease of $1,000,000 from the FY 1994 level. During FY 1994, 92 percent of the full-time trainee positions supported by NCHGR will be terminating. NCHGR does not expect to receive many competitive training applications for FY 1995, therefore, the number of slots has been reduced and the funds shifted to research grants. NCHGR has used the Special Emphasis Research Career Award (SERCA) as the mechanism for encouraging scientists to pursue careers in interdisciplinary genomic research.

The FY 1995 budget request includes $39,387,000 for the Division of Intramural Research. This is an increase of $18,387,000 over the FY 1994 estimate. The mandate of this intramural research program in medical genetics is to take advantage of the resources provided by the Human Genome Project for the study of genetic diseases including their prevention, diagnosis and treatment. This intramural program will provide the NIH with expertise in the latest genome technologies and resources. It is expected to be highly collaborative and will enhance the many research projects in medical genetics already ongoing in other Institutes. The intramural program will carry out research in basic genetic mechanisms, identification of disease genes and their functions, development of new diagnostic technology as well as gene therapy.

The FY 1995 budget request provides $6,339,000 for research management and support activities, an increase of $108,000, 1.73 percent, over the FY 1994 estimate. This increase will provide for basic mandatory increases.

National Center for Human Genome Research

Extramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$100,517,000	$101,470,000	$106,284,000	+$4,814,000

The U.S. Human Genome Project is part of an international effort to develop genetic and physical maps and determine the DNA sequence of the human genome and the genomes of several model organisms. A highly ambitious and focused plan was developed in FY 1990 to outline goals for the first 5 years of the project, FY 1991 through FY 1995. Due to advances in genome technology and a tightly focused effort, the project is on track with respect to these initial goals. These factors plus a much more sophisticated and detailed understanding of what needs to be done and how to do it, led the NCHGR, in collaboration with the Department of Energy, to refine and extend these goals to cover the first 8 years of the project, FY 1991 through FY 1998.

Funding for the extramural program of the NCHGR for the last 5 years:

Year	Amount
FY 1990	$56,727,000
FY 1991	83,681,000
FY 1992	99,836,000
FY 1993	100,517,000
FY 1994	101,470,000

Rationale for the budget request

The FY 1995 request is $106,284,000, an increase of 4.7 percent over the FY 1994 estimate. Current progress and future plans for attaining the new goals of the Human Genome Project are outlined below.

Genetic Mapping

Initial goals met: The initial genetic mapping goal of the Human Genome Project, a map of the human genome with approximately 1,500 "markers," has essentially been achieved through the efforts of a number of investigators both in the United States and abroad. The genetic maps that have been produced during the initial phase of the genome project are proving to be extremely valuable in the analysis of a number of genetic diseases, such as familial early-onset breast cancer, hereditary non-polyposis colorectal cancer, and a form of familial Alzheimer's disease.

Efforts are now being directed toward the next generation of genetic maps, which will be even more useful because the new markers now becoming available are more informative and easier to use. To study the common, complex genetic diseases, e.g. diabetes, cardiovascular diseases, asthma, mental illness, it will be necessary to easily test large numbers of individuals for many markers simultaneously. Thus, genetic markers that can be rapidly analyzed by non-experts in an automated fashion will improve the value of genetic maps even further.

Progress towards mouse map: Major strides have been made in the past year toward the completion of a high resolution genetic map of the mouse genome; over 1,500 reference markers have been incorporated into a framework map as well as over 1,300 markers that identify genes. As expected, there is a great deal of similarity between human and mouse genes (over 900 of the mouse markers have human homologues) and between the human and mouse maps. These correlations will provide insights into human biology and human disease.

Physical Map

Acceleration in physical mapping: Progress in physical mapping has accelerated significantly, largely because the research groups established during the initial stages of the Human Genome Project are now in full production mode. These initial research groups have used automation and developed new technologies to introduce efficiencies into physical mapping. Beyond these early but successful efforts, new technologies that will further accelerate progress continue to be developed: new vectors for cloning DNA have been developed and are being tested, a new integrated robotics system is being built, and innovative mapping strategies continue to evolve.

NCHGR now supports detailed physical mapping efforts on 10 of the 24 human chromosomes and one project that is assembling a low resolution map of the entire human genome. In its first year, this one genome-wide effort has already produced 400 "sequence tagged sites" (STS, a short DNA sequence that uniquely identifies a mapped gene or other marker), and expects to produce a low resolution STS map by 1995. The detailed "higher resolution" maps of several chromosomes (4, 7, 11, X, 22) are nearing completion with isolation of nearly 80 percent of the STSs needed for closure.

Several chromosomes mapped by FY 1995: As these first-generation maps approach closure, new strategies are being developed to evaluate the quality of the maps and to close the remaining gaps. We can expect that, by 1995, the physical maps of chromosomes 4, 7, 11, X, and 22 will be completed, in addition to the maps of chromosomes 21 and Y which were completed last year and are now being defined. We also expect that the maps of several more chromosomes (3, 5, 12, 13) will be near completion by 1995. These achievements will bring us significantly closer to the goal of a map with STS markers every 100,000 base pairs on average.

Physical maps help find disease genes: The maps have had an immediate impact in the field of medical genetics. The pace of finding disease genes has accelerated, in large part because of the success in map assembly and the rapid availability of mapping data. NCHGR encourages early data release and therefore much of the data generated are released before publication and are available online by computer. In addition, several companies are now offering large numbers of human and mouse markers for sale in convenient kits. We can expect that, as the quality of the maps and data access continues to improve, the pace of disease gene discovery will be further expedited.

DNA Sequencing

The next technological challenge: The greatest ongoing challenge for the Human Genome Project, as emphasized in the new 5 year plan, is the development and implementation of technology for rapid, cost-effective sequencing of large genomes. Sequencing is the process of determining the order of the nucleotides, or base pairs, in a DNA molecule. Through DNA sequence analysis scientists are uncovering a wealth of information about human genes, their expression, and their effect on human cell function.

The advancing state of DNA sequencing technology is also evidenced by the formation of several start-up biotechnology companies for which large scale DNA sequencing is an important technological base.

Sequencing model organisms to increase throughput: An NCHGR-supported research team, in collaboration with a research team in Cambridge, England, is continuing to sequence the DNA of the roundworm C. elegans. During the third year of this project, an important milestone for large-scale DNA sequencing was successfully achieved, as each of the two collaborating research teams sequenced more than a million bases of largely contiguous genomic DNA in 1 year. These collaborators have now sequenced a total of 3,000,000 bases of DNA from this model organism, about 3 percent of the genome. During FY 1994, the NCHGR-supported group will attempt to increase this sequence throughput by about 5 fold. In this aggressive project, state-of-the-art DNA sequencing technology is being pushed to the limits and areas of needed technology development and refinement are being defined and pursued.

Sequence of model organisms facilities biological studies: Several other research groups are scaling up to achieve a rate of 1 megabase of DNA sequence per year for other model organisms, including the bacteria that cause tuberculosis and leprosy, the fruit fly Drosophila, and the bacterium E. coli. These organisms continue to be important to scientists as models for understanding human biology, development, and genetic diseases.

Advances in automation: Significant progress has been made toward the development of fully integrated automated sequencing systems. At the start of the Human Genome Project, most sequencing steps were done manually. First generation prototype instruments have now been assembled that perform many of the individual sequencing steps and efforts are beginning to consolidate these instruments into modular systems in which throughput is well-integrated and balanced from front- to back-end. Throughput per machine has increased by about 4-fold since 1990 and further incremental improvements are envisioned to yield an additional 16-fold advance by 1996.

Continued investment in new technologies: Investment is also being made in radically new technologies that could not only facilitate completion of the first human genome sequence but also allow for subsequent sequencing of multiple human genomes as well as genomes of other organisms in a cost-effective manner. Important progress made this year suggest that mass spectrometry could, in the future, replace gel electrophoresis for extremely high throughput sequencing. Moreover, NCHGR-supported research indicates that sequencing by hybridization offers great promise for diagnostic and clinical applications.

Gene Identification

Developing ways to find genes: One of the new 5 year goals of the Human Genome Project is to develop efficient methods for the identification of genes and for the placement of genes on physical maps. The NCHGR currently supports the development of both biochemical and computational approaches to gene identification. Among the former, "exon trapping" (or amplification) is used to isolate genes by exploiting special properties of the DNA that defines the regions that encode proteins. Another new technique, known as "direct cDNA selection," allows the identification of regions of DNA that are expressed as proteins. An entirely different approach to gene identification involves computer analysis. Search algorithms are being developed and refined that can predict the presence of genes within long stretches of sequenced DNA from the order of the bases.

An example of the power of these new approaches was recently demonstrated in the successful search for the Huntington's disease (HD) gene, which took 10 years after the gene had been mapped to a chromosomal region. The search was finally ended by application of the exon amplification technique. Further research is required to make these techniques more efficient and automatable. Emphasis will be on developing a set of complementary technologies that will allow for the exhaustive identification of all genes in the human genome.

Genome Informatics

Genome information management systems: The development of information management systems capable of handling large quantities of experimental data with minimal human intervention also contributed to the rapid progress of many aspects of the Human Genome Project. In FY 1993, several Genome Science and Technology Centers (GESTEC) made significant progress in laboratory data management, particularly in developing systems to support genome-wide physical and genetic mapping projects. The specialized needs of these GESTEC's preclude the use of off-the-shelf commercial systems without significant modification; however, development costs can be substantially reduced if transfer of information management solutions from one GESTEC to another can be accomplished. Thus, the first successful adoption of one GESTEC's data management system by another GESTEC was significant.

Genome databases: Public genome databases will be one of the ultimate products of the Human Genome Project and several have already become important vehicles for publishing and sharing genome mapping and sequencing data. The Genome Data Base (GDB) is a database of human genome information jointly supported by the NCHGR and the Department of Energy. The GDB currently contains information on more than 21,000 genetic markers, an increase of more than 50 percent in FY 1993. Within this number of markers are 4,200 identified genes. The GDB has more than 4,000 registered users.

NCHGR also supports integrated databases containing genome data for the mouse, the fruit fly Drosophila, and the yeast Saccharomyces cerevisiae, (all of which are important model organisms for the Human Genome Project), as well as a national information resource on ethics and human genetics to facilitate scholarly research in the ethical, legal, and social implications of the human genome research.

Genome analysis: The Human Genome Project is developing new and improved analytical methods for deriving biological knowledge from experimental data. For example, computational analyses will be, in many cases, the first tools applied to determination of genetic function. Progress in the development and application of analytical methods continues in, among others, the following areas: analysis of the statistical properties of DNA and protein sequences, prediction of genes and regulatory elements in unannotated DNA sequence, construction and validation of genetic and physical maps, and analysis of raw data from sequencing instruments.

Ethical, Legal and Social Implications of Genomic Research

Policy recommendations developed: Three important sets of policy recommendations that address concerns about possible misuse of genetic information were recently released as a result of NCHGR-sponsored activities.

Guidelines for the protection of families involved in genetic research studies were developed jointly by NCHGR and the NIH Office for Protection from Research Risks (OPRR) and published as a new chapter in the Guidebook that the OPRR provides to every institutional review board in the United States. This document outlines approaches that researchers should use to address privacy and informed consent issues when recruiting families, disclosing research results, and publishing findings. It has already been abstracted and issued as a brochure by the Alliance of Genetic Support Groups for use by the families in their communities.

Recommendations for the protection of health care coverage for individuals and families with genetic health risks was developed by the NIH-DOE Task Force on Genetic Information and Insurance, and conveyed to the White House Task Force on Health Care Reform. The report highlights the growing urgency of the problem of genetic discrimination in health care coverage, outlines the problems with the use of personal genetic information for insurance underwriting purposes, and describes the package of basic benefits required by those at genetic risk.

Guidelines for the protection of patients and users of clinical genetic services were developed by the National Academy of Science/Institute of Medicine Panel on Assessing Genetic Risks and released in November 1993. The panel report offers recommendations for the regulation of genetic diagnostic laboratories, for clinical practice standards in the performance of genetic services, and for public policies governing the use of genetic information by public health authorities.

The ELSI program will continue to address issues of genetic testing and access to health care and employment and provide the results of research done by ELSI grantees to policy makers who are designing and implementing health care reform and the Americans with Disabilities Act.

Interim findings of the cystic fibrosis (CF) studies consortium: One of the first concerted initiatives of the ELSI program was to support, in collaboration with the National Institute of Child Health and Human Development and the National Institute for Nursing Research, a consortium of clinical studies of the psychosocial impact of carrier testing for CF mutations in the general population. These studies have reported their initial findings and recommendations, and a summary is being prepared to convey those findings to the health professions.

Psychosocial impact studies of genetic testing for cancer risk: Based on the experience of the CF studies consortium and the finding of genes that predispose to breast cancer and colon cancer, NCHGR, in collaboration with the National Cancer Institute and the National Institute of Mental Health, is launching an initiative to study the best way to deliver predictive genetic testing for breast and colon cancer risk. These studies will form the basis for recommendations on responsible clinical practices in this area.

Training and Minority Activities

The NCHGR is making progress in recruiting individuals with the type of expertise needed for the development of new technologies that are critical to furthering the goals of the Human Genome Program. The Special Emphasis Research Career Awards program has been successful in attracting physicists, engineers and computer scientists to work in genome laboratories that are intensively involved in developing physical mapping and sequencing technologies. Exposure to molecular biology, both in the form of didactic training and through participating in research projects, will put these individuals in a position to solve the technical problems that are at the interphase of molecular biology and automation. The NCHGR currently supports 6 trainees under this program.

Realizing the importance of increasing the number of minorities who are academically prepared to undertake research careers in the biomedical sciences, NCHGR supports 9 pre-doctoral minority students who are receiving training in research intensive environments, such as Harvard University, University of California, Yale University and MIT. Through the minority supplement program NCHGR is supporting minorities at all career levels from high school students who are working in university laboratories during the summer and after school to faculty who are conducting research projects in their home institutions. The NCHGR currently supports 7 individuals through this program.

National Center for Human Genome Research

Intramural Research

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
3	---	92	$21,000,000	122	$39,387,000	+30	+$18,387,000

The establishment of the NCHGR Division of Intramural Research in FY 1993 and the appropriation of funds in FY 1994 provided tremendous impetus toward the development of a collaborative effort in genome research on the NIH campus aimed at understanding human genetic disease and human gene therapy.

Highlights of this program (whose first staff members were appointed during the summer of 1993) include the recruitment of 85 intramural scientists and support staff and the virtually complete physical establishment of laboratories ranging from Cancer Genetics and Genetic Disease Research to programs which interface with clinical medicine including the Diagnostic Development Branch and Laboratory of Human Gene Transfer. Finally, the establishment and recruitment of investigators to direct a Laboratory of Human Gene Therapy (where the treatment and hopefully the eventual cure of a host of genetic diseases is envisioned as occurring) is also underway.

Funding for the intramural research activity follows:

Year	Amount	FTE
FY 1993	---	3
FY 1994	$21,000,000	92

Rationale for the budget request

The FY 1995 request is $39,387,000, an increase of $18,387,000 over the FY 1994 estimate. A few of the current and planned research activities in the Division of Intramural Research are identified below.

Gene Therapy

While the NCHGR is investigating the application of gene therapy for the treatment of common disease (e.g., cancer and AIDS), it is also actively involved in research relating to potential gene therapies for rare genetic diseases such as adenosine deaminase (ADA) deficiency and the less common form of hemophilia, factor IX deficiency (also know as "Christmas disease" or Hemophilia B). In an active clinical trial for gene therapy for ADA deficiency, NIH researchers had previously shown improvement in patient immunological measures resulting from lymphocyte-directed gene therapy.

Researchers in the new NCHGR intramural program are currently expanding these trials to include gene therapies directed at hematopoietic stem cells derived from peripheral and umbilical cord blood. This research effort is undertaken in collaboration with researchers at the National Cancer Institute and the National Heart, Lung, and Blood Institute and with extramural investigators at various institutions including the Children's Hospital/USC medical school. Research advances in factor IX deficiency are in the preclinical testing phase.

The future plans for gene therapy of rare diseases include implementation of current pre-clinical results on factor IX deficiency to active clinical trials and expansion of stem-cell therapies for ADA patients. Data will be accumulating this year on the initial success or failure of ADA stem-cell gene transfer attempts, and dependent on the outcome, investigates expect to enroll more patients in these trials. For factor IX deficiency, the time frame for initiation of clinical trials is about 2 to 3 years.

A more significant area of investigation that will be essential for the success of future rare disease gene therapy initiatives is basic research into new gene therapy delivery systems. If a delivery system can be developed that can result in higher gene transfer rates and minimize inpatient time, this will greatly expand the potential application of gene therapy to the treatment of rare genetic diseases.

Basic Research on Gene Transfer

Within the Laboratory of Human Gene Transfer, NCHGR, gene therapy for hereditary rare diseases is being approached by the same gene transfer strategies currently employed for more common diseases such as cystic fibrosis and various forms of cancer. In this regard, NCHGR researchers are studying a variety of methodologies including those that employ gene transfer vectors that are viral-based such as adenoviruses or retroviruses and non-viral-based including DNA combined with liposomes. To bring these technologies into clinical practice, the proposed delivery system (including vector and method of administration) must be tested for efficacy and safety in animals as well as human cells. When proof of efficacy and safety are sufficient and the gene transfer vector itself has been approved for human administration, patients can be recruited to participate in clinical trials. The safety and efficacy of new gene delivery strategies are being evaluated and old techniques are being improved in efforts to facilitate the development and implementation of gene delivery systems for human gene therapy.

Cancer Genetics

A major highlight of this program is the recent work of intramural scientists from the Laboratory of Cancer Genetics in collaboration with extramural investigators to identify a gene that leads to colon cancer in as many as 1 in 200 people in the Western world. Because analysis of this gene has revealed a new type of cancer-causing mutation, the discovery is virtually certain to shed light on how many other cancers are activated. This gene, which is responsible for a type of colon cancer called hereditary non-polyposis colorectal cancer (HNPCC), also causes certain cancers of the uterus, ovary, and other organs, making it the gene most common for inherited susceptibility yet cloned in man. It is no exaggeration to state that research of this type would have been considered science fiction ten years ago but with powerful new gene-finding tools generated by the Human Genome Project, it took only six months to go from locating the gene to a region on a chromosome to finding the specific mutation for this form of colon cancer.

Diagnostic Development

The Diagnostic Development Branch will conduct basic research and applied technology development related to the causes and diagnosis of genetic diseases and cancer. Research currently focuses on diseases caused by having more or less than two copies of a gene and on the effect of inheriting a gene from the mother or the father. Studies include investigation of the mechanisms causing chromosomal abnormalities. The consequences of these abnormalities are studied in affected patients to elucidate the pathophysiology of these diseases.

A high priority is the development of new molecular technologies and strategies for the diagnosis of cytogenetic and genetic diseases, including cancer. In this capacity, the DDB will translate the new gene discoveries and automated genome technologies from the basic research laboratory to clinical application as rapidly as possible. New technology will raise new counseling and health policy issues which will be addressed in conjunction with the Medical Genetics Branch of NCHGR. The Diagnostic Development Branch will also take an active role in the transfer of new diagnostic technologies to academic centers and the private medical community by several mechanisms.

Genetic Disease Research

The efforts of scientists within the NCHGR will result in the isolation of human genes causing human genetic disease. Many of these genes will be isolated by the technique known as "positional cloning." This technique allows scientists to identify and isolate disease genes through determining where the disease gene is located on a chromosome rather than by determining what process is abnormal in the disease. Positional cloning is a very powerful method for finding disease genes because it does not require scientists to know what fundamental chemical or physiological process has been disrupted by a disease-causing gene. In fact, discovery of a disease gene through positional cloning may often provide the first real clue as to the mechanism of disease causation.

In the Laboratory of Genetic Disease Research, NCHGR intramural scientists will focus on two major areas of gene discovery and characterization. First, they will work on methods to localize human disease genes on chromosomes by studying how the disease is inherited in families. When a disease tracks through a family, a form of research called linkage analysis allows researchers to determine what portion of which chromosome seems to be inherited along with the disease. This analysis is very straightforward for diseases with simple inheritance patterns, such as cystic fibrosis or sickle cell anemia.

Much more complicated kinds of linkage analysis are need to track the inheritance of more common disorders, such as schizophrenia, atherosclerotic heart disease, and diabetes, where many genes may be contributing to the disease and environmental factors may play a role as well.

The other area of emphasis is on the elucidation of how abnormal genes discovered through positional cloning cause disease. A powerful method for such studies is to create an animal model which carries the mutations in these disease genes and use that animal model to study the mechanism of disease as well as test therapies, including gene therapy. During FY 1995, NCHGR intramural scientists will be using embryonal stem cell technology, a new methodology which allows scientists to introduce mutations into a cultured mouse embryonic cell and then reintroduce that cell back into a mouse embryo, to generate mice carrying these mutations for use as an animal model in studying disease.

Medical Genetics

The Medical Genetics Branch will provide the setting for a program in clinical genetics. Investigators will examine and counsel individuals and families affected by rare genetic disorders of unknown cause(s) in an attempt to (1) identify the genetic contributions to their etiology and (2) to further characterize the natural history of these rare disorders that are currently poorly understood. Protocols will be developed for the improved management of individuals and families having these rare genetic disorders/diseases. Families experiencing inherited forms of cancer, i.e. breast, colon, etc. will also be evaluated and counseled to further the medical understanding of the genetic mechanisms involved. A Family Studies Core will be housed within the Medical Genetics Branch to provide an organized and effective approach to study large families with inherited disorders throughout NIH.

Multidisciplinary research in the psychological sequela experienced by individuals and families identified as having increased risks for certain diseases and/or increased risk for children with genetic disorders will also be conducted. This research will identify the most effective methods of integrating this type of information into an individual's/family's life in the most constructive, least harmful manner.

The Medical Genetics Branch will also be the centerpiece at the NIH of a physician training program in medical genetics, as well as a genetic counselor training program. The development of the clinical research and training programs will be in collaboration with several institutes within NIH, including the National Cancer Institute, the National Institute for Child Health and Human Development, the National Eye Institute, as well as with academic institutions throughout the country.

National Center for Human Genome Research

Research Management and Support

Authorizing Legislation - Section 301 and 487 of the Public Health Service Act. 1995 Authorization: Indefinite

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
52	$5,617,000	61	$6,231,000	61	$6,339,000	--	+$108,000

This activity provides the staff and resources that support the overall administrative and scientific management of the National Center for Human Genome Research. Included under this activity is the Office of the Director, which sets policies, develops scientific, fiscal and management strategies, and provides overall leadership to both the extramural and intramural programs of the NCHGR. Program planning and legislative activities, and computer and network operations come under the purview of the Office of the Director. The Division of Extramural Research plans and develops scientific initiatives in areas that best achieve the goals of the Human Genome Project and studies the ethical, legal, and social implications of human genome research. The Office of Scientific Review coordinates the review of research and research training applications. The Office of Communications serves as the interface between NCHGR and the public, and collaborates with other organizations to disseminate information about the Human Genome Project. The Office of Administrative Management performs a variety of activities associated with the general business operations of the NCHGR, including financial management, human resources management, grants management, and general administrative services.

Funding for the research management and support activity follows:

Year	Amount	FTE
FY 1990	$2,811,000	26
FY 1991	3,717,000	37
FY 1992	4,926,000	44
FY 1993	5,617,000	52
FY 1994	6,231,000	61

Rationale for the Budget Request

The FY 1995 request for the research management and support activity is $6,339,000, an increase of 1.7 percent over the FY 1994 estimate.

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

Detail of Full-Time Equivalent Employment

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director	5	7	7
Office of Admin. Management	26	30	30
Office of Human Genome Communications	2	3	3
Office of Scientific Review	5	6	6
Div. of Extramural Research	14	15	15
Div. of Intramural Research	3	92	122
Total	55	153	183

	Average GS/GM Grade
1989	N/A
1990	9.8
1991	9.8
1992	10.1
1993	10.2
1994	10.1
1995	10.0

NATIONAL INSTITUTES OF HEALTH

National Center for Human Genome Research

New Positions Requested

		1995	
	Grade	Number	Annual Salary
Intramural Research			
Biologists.....................	GM-15	1	75,489
Biologists.....................	GM-14	2	128,358
Cytogeneticist..................	GM-13	1	54,308
Computer Scientist.............	GM-13	1	54,308
Biologists.....................	GS-12	5	228,350
Chemist........................	GS-12	1	45,670
Biologists.....................	GS-11	6	228,642
Biologists.....................	GS-09	4	125,972
Administrative Technician.......	GS-08	1	28,515
Biologists.....................	GS-07	4	102,980
Biologists.....................	GS-05	1	20,784
Purchasing Agent...............	GS-05	1	20,784
Office Automation Clerk.........	GS-03	2	33,102
Total......................		30	1,147,262

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

FY 1995 Budget

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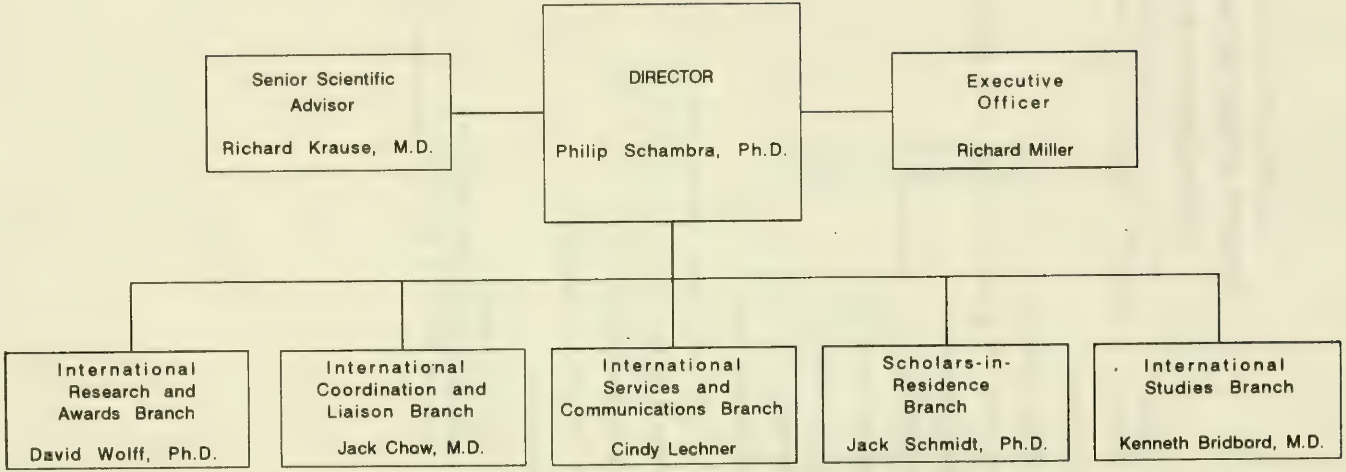
John E. Fogarty International Center

Organizational Chart


DIRECTOR
Philip Schambra, Ph.D.
Senior Scientific Advisor
Richard Krause, M.D.
Executive Officer
Richard Miller
International Research and Awards Branch
David Wolff, Ph.D.
International Coordination and Liaison Branch
Jack Chow, M.D.
International Services and Communications Branch
Cindy Lechner
Scholars-in-Residence Branch
Jack Schmidt, Ph.D.
International Studies Branch
Kenneth Bridbord, M.D.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

For carrying out Sections 301, 307 and title IV of the Public Health Service Act with respect to the John E. Fogarty International Center, [$21,677,000] *$13,745,000 of which $242,000 shall not become available until September 19, 1995.* (Department of Health and Human Services Appropriation Act, 1994.)

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Language Analysis

Language Provision	Explanation
"...Provided, That of the funds made available under this heading, $242,000 shall not become available for obligations until September 19, 1995."	Language has been added to ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

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John E. Fogarty International Center for Advanced Study in the Health Sciences

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$20,002,000	$21,677,000	$13,745,000
Section 511 reduction	-160,000	---	---
Section 513 reduction	-9,000	---	---
Section 216 S&E reduction	-100,000	---	---
Subtotal, adjusted appropriation	19,733,000	21,677,000	13,745,000
Enacted Real Transfer from Other Account for Tuberculosis Research	-18,000	---	---
Comparative transfer to the Office of AIDS Research, NIH for HIV activities	-5,684,000	-8,852,000	---
Subtotal, adjusted budget authority	14,031,000	12,825,000	13,745,000
Unobligated balance, lapsing	-13,000	---	---
Total, Obligations	14,018,000	12,825,000	13,745,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 1993 - $5,191,000; FY 1994 - $9,628,000; FY 1995 - $10,878,000.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	---	---	---	---	2	$936,000
Competing	---	---	2	$900,000	---	---
Subtotal	---	---	2	$900,000	2	$936,000
Other research:						
Other	261	$7,440,000	194	$5,511,000	222	$6,429,000
Total, research grants	261	7,440,000	196	6,411,000	224	7,365,000
1/	FTEs		FTEs		FTEs	
Research Management and Support	75	6,591,000	80	6,414,000	78	6,380,000
Total	75	14,031,000	80	12,825,000	78	13,745,000

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

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John E. Fogarty International Center
for Advanced Study in the Health Sciences

Summary of Changes

1994 Estimated budget authority	$12,825,000
1995 Estimated budget authority	13,745,000
Net change	+920,000

	Current 1994 Estimate Base		Change from Base	
Changes:	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Research Management and Support				
a. Within grade increase		$3,598,000		+43,000
b. Less one day of pay		3,598,000		-14,000
c. Annualization of January 1994 Locality Pay increase		3,598,000		+21,000
d. January 1995 pay increases		3,598,000		+43,000
e. Payment for centrally furnished services		857,000		+35,000
f. Service and supply fund increase		265,000		+21,000
g. Increased cost of supplies, materials, and other mandatory program expenses		1,959,000		+38,000
h. DHHS Working Capital Fund increase		78,000		+1,000
i. Increase for FTS				+1,000
Subtotal, built-in				+189,000
B. Program:				
1. Research Project Grants				
a. Competing		900,000		+36,000
2. Other research				
a. Other research		5,511,000	+28	+918,000
b. Research management and support:		6,414,000	-2	-223,000
Subtotal, program				+731,000
Total changes				+920,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable work years:			
Full-time equivalent employment.....	80	78	-2
Full-time equivalent of overtime and holiday hours................	1	1	---
Average ES Salary....................	$107,000	$107,000	---
Average GM/GS grade..................	9.67	9.80	
Average GM/GS salary.................	36,089	36,494	
Average salary, grades established by act of July 1, 1944 (42 USC 207).	---	---	---
Average salary of ungraded positions..	---	---	---
Personnel compensation:			
Full-time permanent................	$2,670,000	$2,615,000	-$55,000
Other than full-time permanent......	131,000	134,000	+3,000
Other personnel compensation........	113,000	117,000	+4,000
Special personnel service payments..	49,000	51,000	+2,000
Subtotal personnel compensation...	2,963,000	2,917,000	-46,000
Personnel benefits...................	632,000	645,000	+13,000
Benefits for former personnel.........	3,000	3,000	---
Travel and transportation of persons..	95,000	95,000	---
Transportation of things.............	20,000	20,000	---
Rent, communications and utilities....	180,000	180,000	---

	1994 Appropriation	1995 Estimate	Increase or Decrease
Printing and reproduction............	47,000	47,000	---
Other services:			
Consulting services................	40,000	45,000	+5,000
Other Services.....................	1,129,000	1,115,000	-14,000
Purchases from Govt. Accts.........	1,184,000	1,191,000	+7,000
Operation of GOCO's................	---	---	---
R&D Contracts......................	---	---	---
Supplies amd materials...............	66,000	67,000	+1,000
Equipment............................	55,000	55,000	---
Grants, subsidies, and contributions..	6,411,000	7,365,000	+954,000
Total........................	12,825,000	13,745,000	+920,000

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
FIC

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	2,670	2,670	2,615	(55)
11.3	Other than full-time permanent	131	131	134	3
11.5	Other personnel compensation	113	113	117	4
11.8	Special personnel services payments	49	49	51	2
11.9	Subtotal, personnel compensation	2,963	2,963	2,917	(46)
12.1	Civilian personnel benefits	632	632	645	13
13.0	Benefits for former personnel	3	3	3	0
	Subtotal Pay Costs	3,598	3,598	3,565	(33)
21.0	Travel and transportation of persons	95	95	95	0
22.0	Transportation of things	20	20	20	0
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	180	180	180	0
24.0	Printing and reproduction	47	47	47	0
25.0	Other Services	2,353	2,253	2,251	(2)
26.0	Supplies and materials	66	66	67	1
	Subtotal non-pay costs	2,761	2,661	2,660	(1)
	Total Administrative Costs	6,359	6,259	6,225	(34)

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Significant Item in House Appropriations Committee Report

Item	Action Taken or To Be Taken
1994 House Report	
Biodiversity	
The House in its report 103-156, page 69, stated, "The Committee is encouraged by the response to the [International Cooperative Biodiversity Groups (ICBG)] program by the biomedical research community and has included sufficient funds above the President's budget to support additional high priority and meritorious proposals."	The International Cooperative Biodiversity Groups (ICBG) program is sponsored jointly by the National Institutes of Health, the National Science Foundation and the U.S. Agency for International Development. The FIC, who administers the ICBG Program, with funding provided by these agencies, awarded three grants in FY 1993. In response to the House language and with the additional funds provided by the Committee to the FIC, two additional research project grants were awarded in FY 1994.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation.......	Section 301	42§241	Indefinite	$12,825,000	Indefinite	$13,745,000
International Cooperation.........	Section 307	42§242e	Indefinite		Indefinite	
Fogarty International Center.............	Title IV, Part E	42§287b	Indefinite		Indefinite	
Total Budget Authority				12,825,000		13,745,000

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$11,464,000.00	$11,464,000.00	$11,606,000.00	$11,551,000.00
1986 Sequester	---	---	---	(497,000)
1987	11,305,000	11,443,000	11,420,000	11,420,000
1988	11,166,000	12,128,000 2/	11,166,000	15,651,000
1989	11,338,000	16,074,000	16,474,000	15,848,000
1990	10,622,000 3/	15,579,000	15,532,000	15,516,000
1991	16,355,000	18,682,000	17,436,000	17,519,000 4/
1992	19,922,000	19,922,000	19,922,000	19,593,000 5/
1993	20,002,000	19,932,000	19,609,000	19,733,000 6/
1994	19,988,000	22,240,000	19,988,000	21,677,000
1995	13,745,000 7/			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Does not include funding for AIDS research. Consolidated at the Secretary's level.
3/ Does not include HIV-related funds, which were requested in a consolidated amount under the Office of the Assistant Secretary for Health.
4/ Reflects enacted administrative reductions of $540,000.
5/ Reflects enacted administrative reductions of $313,000 and rescission of $16,000.
6/ Reflects enacted administrative reductions of $268,620.
7/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:												
International Research Activities	---	$5,694	---	$7,253	--	$7,440	--	$6,411	--	$7,365	---	$954
Research Management and Support	68	6,460	72	6,728	75	6,578	80	6,414	78	6,380	-2	-34
Subtotal, Obligations	68	12,154	72	13,981	75	14,018	80	12,825	78	13,745	-2	920
Unobligated Balance Lapsing		14		19		13		---		---		---
Total, Budget Authority	68	12,168	72	14,000	75	14,031	80	12,825	78	13,745	-2	920

Justification

John E. Fogarty International Center for Advanced Study in the Health Sciences

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
75	$14,031,000	80	$12,825,000	78	$13,745,000	-2	+920,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the Fogarty International Center (FIC). Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)".

The Fogarty International Center (FIC) was established in 1968 to advance health through international cooperation in medical research, and to serve as the organizational focus for NIH international activities. The FIC is proud of its 25 year history, having fostered research partnerships in over one hundred nations.

The support provided by Congress for these efforts has enabled American scientists to benefit from unique expertise and research resources throughout the world and has resulted in the training of thousands of talented foreign scientists. Many of these scientists continue to collaborate with their American colleagues on major unsolved health problems. The recent discovery of the gene which causes a hereditary form of colon cancer, was made possible through a collaboration between a Finnish scientist trained in the U.S. under the Fogarty International Research Fellowship Program, and his colleagues at Johns Hopkins, Harvard University, and the University of Vermont.

Having contributed to the development of a worldwide base of intellectual capital in the biomedical sciences, the FIC is now building international networks among scientists to meet new and emerging global challenges. In its program priorities, emphasis will be placed on the following goals which will guide the FIC's efforts into the 21st century:

- Creating research and training partnerships between U.S. institutions and research centers in strategic regions of the world to confront global health threats, such as HIV/AIDS and new and resurgent infectious diseases, and the health consequences of unsustainable population growth and environmental damage.

- Developing new and improved therapeutics, vaccines and other medical interventions by enabling U.S. scientists to benefit from unique and specialized research talents and resources in other countries.

- Preparing the current and future generation of American scientists to excel in a global environment, and increasing the participation of underrepresented minorities in global research and training efforts.

- Advancing the future directions of NIH research and policy through scholarly studies on emerging biomedical challenges, in furtherance of FIC's founding mandate as an international center of advanced studies.

These goals are further elaborated in the following sections:

Mobilize International Research Efforts Against Global Health Threats

The eradication of dreaded diseases will not only improve the quality of our lives, it will also save our nation money. For example, when a scientific breakthrough occurs, perhaps in the form of a vaccine that is relatively inexpensive and easy to deliver, it is usually less expensive to prevent than to cure an illness. Many promising avenues in prevention research, such as a children's vaccine to combat a multitude of childhood infections, will require international cooperative efforts. Investment in pioneering international research will influence our capacity to address the growing national need to contain health care costs.

The recent threat of the Hanta virus outbreak in the Four Corners region of the Southwest, which then spread to other states, provides a good example of the importance of rapid identification of new and or re-emerging infections. Our capacity to identify rapidly the Hanta virus outbreak was the result of international studies in regions of East Asia where the virus is endemic.

Health and Population--Global health threats such as new epidemics and environmentally related diseases are greatly exacerbated by population growth which outpaces economic development. In support of future strategies for sustainable development, the FIC will initiate an International Research and Training Program on Health and Population. International partnerships will be fostered between U.S. universities and research institutions and counterparts in strategic regions of the world in areas related to child and maternal health, to include studies on reproductive health, determinants and consequences of population growth, demographic change and contraceptive development and evaluation.

Advance Science Through International Cooperation

The essence of international cooperation in medical research is the exchange of information and ideas that speed progress. Collaborative research enables American scientists to benefit from innovative methods and technologies and unique research resources and environments on a global basis. The FIC supports important collaborative research activities through a number of well-established research programs such as the Senior International Fellowship (SIF) and Scholars-in-Residence Programs. The SIF program will be extended to provide opportunities for junior American postdoctoral scientists to conduct research abroad. The FIC has also established programs to enhance collaborative research activities in selected regions of the world to accommodate the ever-changing global situation. These programs--the FIC Regional Initiatives in Russia, Eastern Europe and Latin America--are important factors in our commitment to research efforts worldwide.

Regional Initiatives in Russia, Eastern Europe and Latin America--The FIC initially established regional research cooperation with Latin America, and then, during the early stages of the restructuring in Russia and Eastern Europe, to those regions as well. The Fogarty International Research Collaboration Award (FIRCA) provides small grants to American researchers to support cooperative studies with leading scientists in these regions. The FIRCA program is expected to pioneer scientific cooperation in other geographic regions, as well as in emerging fields of science concerned with global health threats.

Biodiversity Program for Drug Development--Developing new drugs from natural products not only may produce treatments for diseases like cancer and AIDS, but could also promote economic growth in emerging nations through sustainable harvests. In the United States, one-quarter of all pharmaceuticals are substances extracted from plants, and another 13 percent of drugs are derived from bacteria and other microorganisms, yet only a tiny fraction of the world's biological wealth has been studied for potential therapeutic benefit.

The International Cooperative Biodiversity Groups Program is an interagency program supported by the U.S. Agency for International Development, the National Science Foundation, and the NIH. The Program joins scientists and institutions in the United States with their counterparts in Argentina, Cameroon, Chile, Costa Rica, Mexico and Suriname, to identify new bioactive natural products from plant and marine extracts and microorganisms and to help preserve the rich natural diversity of rain forests and oceans. The program is designed to promote both economic growth and ecological conservation by demonstrating the value of biological resources from which natural products are derived. Using funds provided by the three agencies, the FIC awarded three grants in FY 1993 and, with funding provided to the FIC in FY 1994, two additional grants were awarded. These efforts will continue in FY 1995.

Develop Human Resources to Meet Global Research Challenges

FIC programs assist in preparing the current and future generations of biomedical scientists to function and excel in a global environment. In order to continue the commitment to this important goal, within today's limited resources and ever-changing global research atmosphere, programs must be evaluated and modified to most effectively use available resources.

Research Opportunities for Scientists from Developing Nations--The International Research Fellowship (IRF) Program, the most longstanding of FIC programs, was developed to assist in rebuilding the science base in post-World War II Europe by enabling young European and Japanese researchers to train and conduct cooperative research in U.S. institutions. Over its 35 year history, the IRF has contributed to the creation of an advanced research capacity in developed countries of the world. Today, however, there is an increasing need to provide research and training opportunities for scientists from developing nations. Such efforts are needed to reverse the deepening disparity in health and economic status between the industrialized and developing world, and combat new and re-emerging infections which often arise in these areas. Thus, the FIC will refocus the IRF program and shift the geographic emphasis from developed countries to developing nations. This new emphasis will provide greater opportunities for scientists with limited possibilities for state-of-the-art training, and expand linkages to regions of the world that are key to the management of HIV/AIDS and emerging infectious diseases, environmental health, population and other transnational challenges.

International Science Opportunities for Underrepresented Minorities--The success of the U.S. in ensuring a continuing and balanced supply of highly trained scientists depends on our capacity to recruit underrepresented minorities into the biomedical research professions. The FIC, in collaboration with the Office of Research on Minority Health (ORMH), has examined what could be done to attract more minority participation in the sciences, and explored possible targeted opportunities to enhance minority participation.

As a result of these efforts, the Minority International Research Training (MIRT) Program was established to encourage minority students to pursue degrees in the biological sciences, and scientific careers, by broadening their undergraduate and graduate education at foreign universities. The program also seeks to enable minority research faculty to extend their research pursuits at leading foreign institutions. The goal is to increase the number of minority students pursuing a career in international health research. With funding support from the ORMH, the FIC awarded 15 MIRT grants in FY 1993 to U.S. institutions.

Provide Leadership in International Science Policy and Research Strategies

The internationalization of science requires an ongoing analysis of the global dimensions of national science policy. A leading function of the FIC is to provide leadership and direction on international policy issues that affect the course and conduct of biomedical science.

The FIC plays an instrumental role in international policy analysis and formulation at the NIH, Departmental and interagency levels, providing advice to the NIH leadership on a variety of international issues that affects the course and conduct of biomedical science. These have included analyses and recommendations on intellectual property rights, technology transfer and commercialization issues, international competitiveness, and immigration statutes and regulations. As an example, FIC staff took the initiative in tracking negotiations on the General Agreement on Tariffs and Trade (GATT) related to research subsidies and were able to call attention to provisions that could hinder many of NIH's technology transfer programs. By working with the NIH Director's Office and other agencies, the FIC helped bring this issue to the attention of the appropriate officials in the Administration which resulted in beneficial changes in the GATT research subsidy provisions.

The President's appropriation request of $13,745,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the Fogarty International Center during the last five years has been as follows:

Year	Amount	FTE
FY 1990	$10,758,000	60
FY 1991	12,168,000	68
FY 1992	14,000,000	72
FY 1993	14,031,000	75
FY 1994	12,825,000	80

Purpose and Method of Operation

The FIC carries out the extramural research and training components of its four strategic goals through a number of international fellowship and award programs that provide research opportunities in a wide range of biomedical research areas.

FIC also funds several scientific programs and services in support of the NIH intramural research programs through its Research and Management Support (RMS) activity. These programs include the Health Scientist Exchange Programs, the U.S.-Japan Summer Institute Program, the Human Frontier Science Program, and administrative support for the NIH Visiting Program.

Overall Budget Policy

The FY 1995 budget request for the FIC non-AIDS programs is $13,745,000, a net increase of $920,000 over the comparable FY 1994 level of $12,825,000. The request includes 78 FTEs, a decrease of 2 from the FY 1994 level of 80.

A total of $936,000 is requested in Research Project Grants, an increase of $36,000 over FY 1994, for the continued support of the International Cooperative Biodiversity Groups Program.

A total of $6,429,000 is requested in Other Research, reflecting a net increase of $918,000 from the FY 1994 level. The net increase of $918,000 consists of an increase of $637,000 for the Fogarty International Research Collaboration Awards Program; $379,000 for the Senior International Research Fellowships Program; $400,000 for the Health and Population Program; and $65,000 for the Scholars-in-Residence Program; offset by a reduction of $468,000 in the International Research Fellowship Program and $95,000 in the Environmental Fellowship Program. The total number of awards for FY 1995 is 224, an increase of 28 awards from the FY 1994 estimate of 196.

In accordance with the principles of the NIH Cost Management Plan, the average cost of the research project grant awards received a four percent increase over the direct cost level of the FY 1994 amount.

A total of $6,380,000 will be available in the Research Management and Support mechanism, which reflects a net decrease of $34,000 from FY 1994. The budget request reflects reductions in staffing and administrative costs.

NATIONAL INSTITUTES OF HEALTH
Fogarty International Center

Distribution of Funds by Program Goals
(Dollars in thousands)

	FY 1993		FY 1994		FY 1995	
	No.	Amount	No.	Amount	No.	Amount
MOBILIZE INT'L. RESEARCH EFFORTS AGAINST GLOBAL HEALTH THREATS	0	0	0	0	4	400
Health and Population	0	0	0	0	4	400
ADVANCE SCIENCE THROUGH INTERNATIONAL COOPERATION	138	4,600	123	4,961	166	6,078
Fogarty International Research Collaboration Awards						
Extramural						
Noncompeting	29	684	61	1,399	51	1,200
Competing	55	1,275	22	533	59	1,369
Subtotal	84	1,959	83	1,932	110	2,569
Intramural Research		90		0		0
International Cooperative Biodiversity Groups	0	0	2	900	2	936
Senior International Fellowships						
Noncompeting	15	224	16	244	11	171
Competing	34	830	17	418	35	870
Subtotal	49	1,054	33	662	46	1,041
Scholars-in-Residence						
Noncompeting/Supplements	(21)	463	(17)	444	(12)	398
Competing	5	155	5	156	8	267
Subtotal	5	618	5	600	8	665
Scientist Exchange Programs		224		217		217
Conferences and Workshops		155		150		150
Human Frontier Science Program		500		500		500
DEVELOP HUMAN RESOURCES TO MEET GLOBAL RESEARCH CHALLENGES	123	3,854	73	2,377	54	1,814
International Research Fellowships						
Noncompeting	52	1,674	39	1,273	21	698
Competing	60	1,973	29	949	33	1,056
Subtotal	112	3,647	68	2,222	54	1,754
Neuroscience Fellowships	6	72		0		0
Environmental Fellowships	5	90	5	95		0
Japan Summer Institute		45		60		60
PROVIDE LEADERSHIP IN INT'L SCIENCE POLICY AND RESEARCH STRATEGIES		5,577		5,487		5,453
FIC Services to NIH Science Programs		1,897		1,884		1.884
FIC Program Administration		3,680		3,603		[illegible]
TOTAL		14,031		12,825		1[illegible],745

John E. Fogarty International Center
for Advanced Study in the Health Sciences

International Research Activities

Authorizing Legislation - Sections 301 and 307 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$7,440,000	$6,411,000	$7,365,000	$954,000

The FIC supports extramural research and research training through its Fogarty International Research Collaboration Award, International Research Fellowship and Senior International Fellowship Programs, Scholars-in-Residence Program, and the International Cooperative Biodiversity Groups Program.

The Fogarty International Research Collaboration Award (FIRCA) program is a small grants program established to facilitate collaboration between American scientists and scientists from Latin America and Eastern Europe (including the former Soviet Union) for research in scientific areas of high priority in the U.S. and in the region, especially where unusual opportunities exist for population-based research.

The International Cooperative Biodiversity Group (ICBG) Program was established in FY 1993. The projects supported by this program include the screening and cataloguing of plants, insects and related species, the examination of traditional medicine practices from indigenous cultures, and training and career development for scientists from cooperating nations. The two ICBG awards using funds appropriated to the FIC in FY 1994 will support research that includes: the evaluation of plant extracts for use against malaria, leishmaniasis, and trichomonad infections; the identification of new antiparasitic drugs; and the evaluation of the effectiveness and safety of plants used by traditional medicine practitioners through testing for three conditions, tumors, leishmaniasis, and diarrheal diseases.

Long-standing programs, such as the International Research Fellowship, the Senior International Fellowship and the Scholars-in-Residence programs, strengthen international research efforts by supporting Americans abroad and foreign scientists in the U.S. These programs have been the foundation of the FIC's extramural contributions and continue to provide a broad array of research and research training opportunities.

The President's appropriation request of $7,365,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the Fogarty International Center during the last five years has been as follows:

Year	Amount
FY 1990	$5,299,000
FY 1991	5,694,000
FY 1992	7,253,000
FY 1993	7,440,000
FY 1994	6,411,000

Rationale for the Budget Request

With the FY 1995 extramural request, these funds will provide support for the FIC's International Research Activities in the amount of $7,365,000, a net increase of $954,000 or 14.9% over the FY 1994 estimate of $6,411,000. The net consists of $637,000 for the Fogarty International Research Collaboration Awards Program; $379,000 for the Senior International Fellowship Program; $400,000 for the Health and Population Program; $65,000 for the Scholars-in-Residence Program and $36,000 for the International Cooperative Biodiversity Groups Program; offset by a reduction of $468,000 in the International Research Fellowship Program and $95,000 in the Environmental Fellowship Program.

Representative examples of research projects that will continue to be funded by the International Research Activities Programs follow.

Molecular Mechanisms in Disease Control and Prevention--During the last decade, many short protein molecules with high biological activity--so-called regulatory peptides--have been detected and identified. Several of these peptides are responsible for the transmission of electrical signals between nerve cells in the brain, or between nerve fibers and various tissues in the body, and serve as the mediators of intracellular communication in the central and peripheral nervous systems. Using molecular biology techniques, a Scholar-in-Residence from Sweden has identified the genes that regulate the formation and function of these peptides. This advance in our understanding of the ways in which genes control motor and mental functions could eventually make a number of neurological and psychiatric disorders responsive to gene therapy.

Knowledge about the mechanism of virus assembly is important for the design of new drugs that would prevent viral production in infected cells. The manufacture of a complete virus is associated with the breakdown of specific proteins by an enzyme called viral proteinase. With support from the Fogarty International Research Collaboration Award Program, U.S. investigators working with scientists from the Czech Republic are analyzing the precise function of this proteinase. Once this is successful, drugs can then be designed that block this enzyme to treat the HIV infection.

Drug Development through Natural Products--A search is underway among the traditional medicines from around the world for the discovery of new anticancer drugs. An International Research Fellow from Nigeria has analyzed plant extracts and identified four species with anticancer activity. In laboratory tests, the plant extracts were active against tissue cultures of human cancer cells including colon, fibrosarcoma, lung, and melanoma cancers. The next step is to conduct tests in animals to determine which may prevent cancer growth.

Kidney Disease/Hypertension--A major function of the kidney is maintaining a healthy concentration of salt in the blood and body tissues. Disruption of this function occurs in both kidney disease and hypertension. Recent studies have demonstrated an influence of the nervous system on this kidney function in both health and disease. Collaboration between a Senior International Fellow and Swiss scientists are looking closely at the chemical basis of this influence of the nervous system in an effort to develop new methods of treatment.

Infant Mortality/Prevention--Delivery of a normal infant at birth depends on fetal health during pregnancy. New methods are needed to gauge the health of the fetus which lives in a liquid environment provided by the amniotic fluid. A Senior International Fellow in collaboration with Australian scientists has developed a new technique to learn how the fetus can survive "underwater" and to determine if abnormal amniotic conditions of the mother are detrimental to the survival of the fetus.

Mental Health--Patients with a major depression illness have a high risk of both attempted and successful suicide. Prevention of suicide depends on early identification and treatment of those most likely at risk. Recent studies suggest that levels of serotonin, a neurotransmitter in the spinal fluid, can be used to identify the severe clinical depression that is associated with suicide. An International Research Fellow from Ireland has provided further evidence for this hypothesis, and suggested new treatment strategies likely to induce early remission of suicidal symptoms.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Research Management and Support

Authorizing Legislation - Sections 301 and 307 of the Public Health Service Act. 1995 Authorization: Indefinite.

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
75	$6,591,000	80	$6,414,000	78	$6,380,000	-2	-$34,000

A number of distinctive programs are funded through the Research Management and Support (RMS) mechanism, providing resources to support several FIC science programs and services to NIH science programs as well. The Health Scientist Exchange Programs, the Human Frontier Science Program and the U.S.-Japan Summer Institute Program are all supported within the RMS mechanism, as well as the International Coordination and Liaison Program and scientific conferences and workshops.

RMS funds also support the FIC International Services and Communications Program which administers the NIH Visiting Program through which foreign postdoctoral scientists and senior foreign scientists conduct research in NIH laboratories in collaboration with their American colleagues.

These endeavors further contribute to international research collaboration by promoting contacts and cooperation between health professionals and biomedical scientists in the U.S. and participating countries. In addition to FIC program activities, RMS funds support all FIC staff and provide for the overall scientific management operations and administrative requirements of the Center, including oversight of research collaboration under 82 bilateral agreements with some 40 countries.

The President's appropriation request of $6,380,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the Fogarty International Center during the last 5 years has been as follows:

Year	Amount	FTE
FY 1990	$5,319,000	60
FY 1991	6,474,000	68
FY 1992	6,747,000	72
FY 1993	6,591,000	75
FY 1994	6,414,000	80

Rationale for the Budget Request

The FY 1995 budget request for RMS is $6,380,000, which represents a decrease of $34,000 from the FY 1994 appropriation. Core program activities are covered in the RMS section along with administrative and program operations costs. The following examples are illustrative of some of the activities that will be funded through this mechanism.

Science Programs--Through the Health Scientist Exchange Programs, the FIC supported research at Johns Hopkins University where researchers from Bulgaria and the U.S. worked together to discover a new method for analysis of electrocardiogram (ECG) records. During the early stages of acute angina, conventional electrocardiographic analysis does not rapidly capture and localize ischemic injury. Their collaborative research may help detect damage to the heart, including transient or permanent changes resulting from injury to the heart before and after angioplasty and at other points where the heart may suffer damage.

Policy Development Activities--The FIC remains committed to its efforts in this broad and important area, as these activities can affect the NIH and broader U.S. interests as well. The following types of policy development activities and services will be continued in FY 1995.

The NIH is involved in a new initiative by the Department of State to increase U.S.-Japan cooperation in AIDS prevention. This initiative also seeks to promote U.S.-Japan cooperation in other global areas of mutual interest including population, environmental health, and disaster prevention and assistance. The entire initiative, known as the Global Cooperation Framework, was announced by President Clinton and former Prime Minister Miyazawa at their July 1993 Tokyo summit. The FIC is working closely with the Office of AIDS Research and other NIH components, the U.S. Agency for International Development, and the Department of State to work out details of cooperative activities and their implementation.

With support from the State Department, the FIC recently sponsored a conference in Cairo on Environmental Health Issues in the Middle East. The goals of the workshop were to bring together leading scientists from throughout the Middle East to assess environmental health risks in the region, to develop working relationships, and to provide a framework for future collaborations. This conference was the first of its kind to bring scientists from Bahrain, Gaza, Egypt, Israel, Jordan, Kuwait, Lebanon, Saudi Arabia, the United Arab Emirates, the U.S. and the West Bank to address common environmental health problems. As a result of this conference, an Environmental Health Committee for the Middle East was established to encourage communication and to promote regional efforts to address environmental health problems. A framework for cooperation is under development.

Program Services--The International Services and Communications Program provides overall administrative and technical support for the NIH Visiting Foreign Scientist Program. During FY 1993, the FIC arranged for the participation of over 3,100 foreign scientists in the intramural laboratories of the NIH institutes and other PHS agencies located on the NIH campus, providing visa, immigration, and other administrative support and advice for the foreign scientists. In addition to the normal program operative procedures, FIC staff participated in discussions on important immigration policy issues relating to the NIH on the Exchange Visitor Program, the Chinese Student Protection Act, NAFTA, and the most recent changes and interpretations of immigration law and policy, including the resolution of several NIH concerns on immigration procedures that affect the NIH directly.

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NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of the Director.......	22	23	21
Scholars-in-Residence Branch....................	5	5	5
International Services and Communications Branch......	19	22	22
International Studies Branch....................	6	6	6
International Research and Awards Branch.............	10	10	10
International Coordination and Liaison Branch.........	13	14	14
Total FIC.................	75	80	78

Average GS/GM Grade	
1990...	9.80
1991...	11.15
1992...	9.00
1993...	9.60
1994...	9.67
1995...	9.80

NOTE: Includes FTEs associated with HIV Research Activities. Funds to support these FTE's are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

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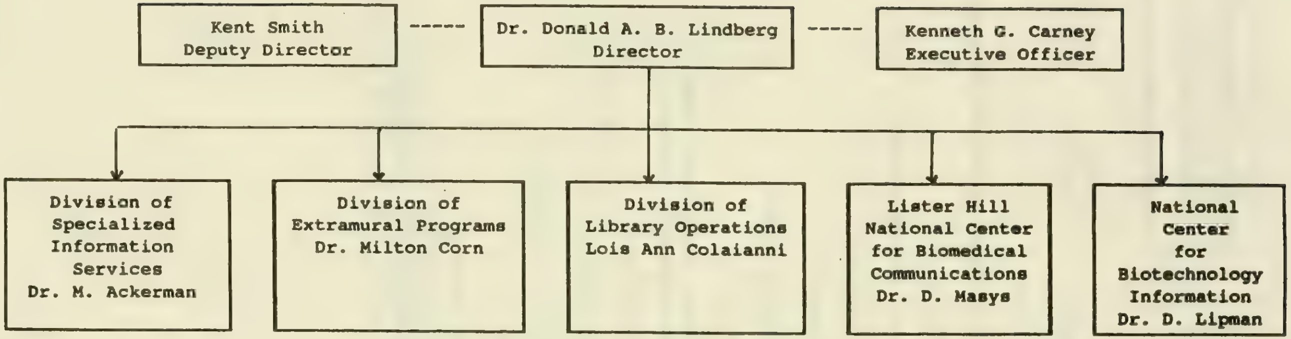
NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Organization Structure


Kent Smith
Deputy Director
Dr. Donald A. B. Lindberg
Director
Kenneth G. Carney
Executive Officer
Division of Specialized Information Services
Dr. M. Ackerman
Division of Extramural Programs
Dr. Milton Corn
Division of Library Operations
Lois Ann Colaianni
Lister Hill National Center for Biomedical Communications
Dr. D. Masys
National Center for Biotechnology Information
Dr. D. Lipman

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

For carrying out section 301 and title IV of the Public Health Service Act with respect to the Library, [$119,981,000] $135,330,000 *of which $1,450,000 shall not become available for obligation until September 19, 1995*. *(Department of Health and Human Services Appropriation Act, 1994.)*

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Language Analysis

Language Provision	Explanation
"of which $1,450,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlay limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation..................	$105,024,000	$119,981,000	$135,330,000
Section 216 reduction..........	-516,000	---	---
Section 511 reduction..........	-840,000	---	---
Section 513 reduction..........	-29,000	---	---
Subtotal, adjusted appropriation..............	103,639,000	119,981,000	135,330,000
Comparative transfer from:			
National Institute of General Medical Sciences for GENBANK.................	---	---	---
Comparative transfer to:			
Office of AIDS Research, NIH for HIV Activities..........	-1,101,000	-3,082,000	
Real transfer between ICDS for Tuberculosis.......	-26,000	---	---
Subtotal, adjusted budget authority..........	102,512,000	116,899,000	135,330,000
Unobligated balance lapsing...	-117,000	---	
Total, Obligations..........	102,395,000	116,899,000	135,330,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1993: $11,893,000; FY 1994: $11,814,000; FY 1995: $11,814,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Extramural Programs:						
Grants:						
Noncompeting...............	66	$17,508,000	62	$14,984,000	53	$15,440,000
Competing..................	34	3,544,000	44	6,835,000	50	8,490,000
Subtotal, Grants...........	100	21,052,000	106	21,819,000	103	23,930,000
Contracts:						
Noncompeting................	8	5,500,000	8	6,000,000	8	6,168,000
Competing...................	--	---	--	---	--	---
Subtotal, Contracts........	8	5,500,000	8	6,000,000	8	6,168,000
Total, Extramural......	108	26,552,000	114	27,819,000	111	30,098,000
	FTEs		FTEs		FTEs	
Intramural Programs:						
Library Operations...........	360	38,580,000	356	45,708,000	347	47,535,000
Lister Hill Center...........	86	14,173,000	85	20,422,000	83	34,099,000
Biotechnology Center.........	37	10,167,000	36	10,066,000	35	10,354,000
Toxicology Information.......	38	4,945,000	37	4,894,000	36	5,077,000
Total, Intramural......	521	67,865,000	514	81,090,000	501	97,065,000
Research Management and Support	104	8,095,000	100	7,990,000	98	8,167,000
Total Budget Authority.......	625	102,512,000	614	116,899,000	599	135,330,000

Note: Includes 10 FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Summary of Changes

1994 Appropriation	$116,899,000
1995 Estimated budget authority	135,330,000
Net Change	+18,431,000

	1994 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural Programs				
a. Within grade increase		$27,130,000		+$387,000
b. Annualization of January 1994 localtiy pay increase		27,130,000		+256,000
c. One less day of pay		27,130,000		-104,000
d. Federal employ. compensation		27,130,000		+23,000
e. January 1995 pay increases		27,130,000		+332,000
f. FTS increase		273,000		+8,000
g. Service and supply fund increase		1,302,000		+73,000
h. Payment for centrally furnished services		9,360,000		+385,000
i. Increased cost of supplies, materials, literature and other expenses		44,600,000		+1,599,000
Subtotal				+2,959,000
2. Research Management & Support:				
a. Within grade increase		5,642,000		+80,000
b. Annualization of January 1994 locality pay increase		5,642,000		+54,000
c. One less day of pay		5,642,000		-22,000
d. January 1995 pay increases		5,642,000		+70,000
e. Service and supply fund increase		69,000		+4,000
f. Increased cost of supplies, materials, literature and other expenses		2,348,000		+63,000
g. DHHS working capital fund		207,000		+2,000
Subtotal				+251,000

Summary of Changes--continued

	1994 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
B. Program:	No.	Amount	No.	Amount
1. Grants:				
a. Noncompeting............	62	14,984,000	-9	+456,000
b. Competing...............	44	6,835,000	+6	+1,655,000
Total.....................	106	21,819,000	-3	+2,111,000
2. Contracts:				
a. Noncompeting............	8	6,000,000	---	+168,000
b. Competing...............	---	---	---	---
3. Intramural Programs..........	514	81,090,000	-13	+13,016,000
4. Research Management & Support	100	7,990,000	-2	-74,000
Subtotal................				+15,221,000
Total changes...........				+18,431,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time equivalent employment....	614	599	-15
Full-time equivalent of overtime and holiday hours................	6	6	---
Average SES salary..................	$108,399	$110,800	+$2,401
Average GM/GS grade.................	11.0	11.0	---
Average GM/GS salary................	39,719	40,599	+880
Average salary, grades est. by act of July 1, 1944 (42 U.S.C. 207)....	73,971	75,641	+1,670
Average salary of ungraded positions........................	0	0	---
Personnel compensation:			
Permanent positions................	$24,642,000	$24,654,000	+12,000
Positions other than permanent.....	2,235,000	2,238,000	+3,000
Other personnel compensation.......	645,000	646,000	+1,000
Special personal services payments.	50,000	50,000	---
Subtotal, personnel compensation.	27,572,000	27,588,000	+16,000
Personnel benefits..................	5,175,000	5,202,000	+27,000
Benefits for former personnel........	25,000	25,000	---
Travel and transportation of persons.	453,000	463,000	+10,000
Transportation of things.............	106,000	117,000	+11,000
Rental Payments to Others (23.2).....	51,000	58,000	+7,000
Communications, Utilities, and Miscellaneous Charges (23.3).......	1,045,000	1,130,000	+85,000
Printing and reproduction...........	1,199,000	1,372,000	+173,000

	1994 Appropriation	1995 Estimate	Increase or Decrease
Other services:			
Consulting Services................	375,000	398,000	+23,000
Other..............................	30,598,000	42,583,000	+11,985,000
Purchases from Govt. Accts..........	13,136,000	16,190,000	+3,054,000
Operation of GOCOs.................	0	0	---
R&D Contracts......................	6,000,000	6,168,000	+168,000
Supplies and materials...............	548,000	583,000	+35,000
Equipment...........................	8,797,000	9,523,000	+726,000
Grants, subsidies & contributions.....	21,819,000	23,930,000	+2,111,000
Total budget authority by object	116,899,000	135,330,000	+18,431,000

Note: Includes FTEs associated with HIV Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

National Institutes of Health
Administrative Costs
Budget Authority
NLM

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	24,642	24,642	24,654	12
11.3	Other than full-time permanent	2,235	2,235	2,238	3
11.5	Other personnel compensation	695	645	646	1
11.8	Special personnel services payments	0	50	50	0
11.9	Subtotal, personnel compensation	27,572	27,572	27,588	16
12.1	Civilian personnel benefits	5,175	5,175	5,202	27
13.0	Benefits for former personnel	25	25	25	0
	Subtotal Pay Costs	32,772	32,772	32,815	43
21.0	Travel and transportation of persons	453	453	463	10
22.0	Transportation of things	106	106	117	11
23.2	Rental payments to others	51	51	58	7
23.3	Communications, utilities, and miscellaneous charges	1,045	1,045	1,130	85
24.0	Printing and reproduction	1,199	1,199	1,372	173
25.0	Other Services	56,410	43,356	58,618	15,262
26.0	Supplies and materials	548	548	583	35
	Subtotal non-pay costs	59,812	46,758	62,341	15,583
	Total Administrative Costs	92,584	79,530	95,156	15,626

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Significant Items in the Senate Appropriations Committee Reports

Item	Action Taken or to be Taken
1994 Senate Report	
High Performance Computing and Communications	
1. The Senate in its report, page 122, stated, "The Committee is pleased to see a lead role being taken by the National Institutes of Health, and particularly the National Library of Medicine, in the development of the national information infrastructure for health care, and applauds the library's effective leadership in coordinating the HPCC effort with NIH and among Federal science agencies. The Committee encourages NLM and the Advanced Research Projects Agency (ARPA) of the Department of Defense (DOD) to continue the cosponsorship of research project proposals in health care information technology".	1. NIH and particularly the NLM are continuing their institutional interest in development of a national information infrastructure for health care. NLM provides the leadership and coordination of the HPCC efforts of the NIH and the Federal Government. The coordination of new initiatives with ARPA is an important aspect of the inter-agency effort. The NLM and ARPA have signed a memorandum of understanding to jointly support research proposals in health care information technology. NLM also has similar arrangements with the NCI and AHCPR.
Outreach	
2. The Senate in its report, page 122, stated, "The Committee is aware of the Mississippi Health Sciences Informational Network's success in providing health sciences information and encourages the National Library of Medicine to consider expanding its successful efforts".	2. Outreach continues to be one of NLM's highest priorities, particularly in reaching underserved populations in rural areas.
3. The Senate in its report, page 122, stated, "The Committee enthusiastically supports the NLM's efforts toward improving health care information sharing among clinicians, researchers, educators, and other health professionals	3. The NLM will be supporting projects applying HPCC technologies in the health care sector. A major emphasis will be in creating testbed networks for linking hospitals, clinics, doctor's offices, medical

through the implementation of a national information superhighway. Improving communication among members of the health care community not only benefits patient care, but also decreases overall health care expenditures. In order to maximize the productivity of these activities, the Committee urges that they be effectively coordinated through the use of medical librarians and other health information specialists".

schools, and medical libraries to enable health care providers and researchers to share medical data and imagery. Medical librarians will have a key role in these experiments and in future systems. In order to assure that our society benefits from the skills of properly trained medical librarians, and that they have an opportunity to engage in the most important work concerning information and health care, NLM's Board of Regents has launched a Planning Panel on the Education and Training of Health Science Librarians that will issue a report with recommendations for NLM and others later this year.

NATIONAL INSTITUES OF HEALTH

National Library of Medicine

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1993 Amount Authorized	1994 Appropriation	1994 Amount Authorized	1995 Budget Request
Research Investigation...	Title III, Part A Section 301	42 421	Indefinite		Indefinite	
National Library Medicine........	Title IV, Part D Section 465-478a	42 286	Indefinite	$116,899,000	$150,000,000	$135,330,000
Total Budget Authority				116,899,000		135,330,000

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Appropriation History

Year	Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$53,320,000	$46,972,000 2/	$60,000,000	$57,808,000
1986 Sequester				-2,486,000
1987	56,408,000	61,588,000	62,088,000	61,838,000
1988	64,399,000	71,465,000	70,399,000	67,910,000
1989	70,626,000	64,836,000 2/	70,626,000	73,731,000
1990	78,729,000	83,311,000	80,729,000	82,932,000 3/
1990 Sequester				-1,071,000
1991	89,916,000	80,725,000	94,416,000	91,408,000
1991 Sequester				-1,000
1992	100,554,000	99,565,000	100,549,000	99,323,000 4/
1993	107,561,000	103,923,000	103,923,000	103,639,000 5/
1994	133,349,000	118,481,000	120,481,000	119,981,000
1995	135,330,000 6/			

1/ Reflects enacted supplementals, recissions and reappropriations.

2/ Excludes funds for Medical Library Assistance Act programs not considered.

3/ Excludes enacted administrative reduction of $379,000.

4/ Excludes enacted administrative reduction of $980,000.

5/ Excludes enacted administrative reduction of $1,385,000.

6/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the HIV Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Budget Authority by Activity

(Dollars in thousands)

	1991 Actual		1992 Actual		1993 Actual		1994 Appropriation		1995 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Programs:												
Med'l. Lib. Assistance.		$14,680		$15,071		$15,090		$15,683		$16,622		$939
PHS 301................		10,800		11,667		11,459		12,136		13,476		1,340
Total, Extramural....		25,480		26,738		26,549		27,819		30,098		2,279
Intramural Programs												
Library Operations.....	352	35,820	364	37,799	360	38,574	356	45,708	347	47,535	-9	1,827
Lister Hill Center.....	90	11,735	90	14,236	86	14,142	85	20,422	83	34,099	-2	13,677
Biotechnology Center...	32	5,694	38	6,459	37	10,156	36	10,066	35	10,354	-1	288
Toxicology Information.	41	4,491	39	4,722	38	4,936	37	4,894	36	5,077	-1	183
Total, Intramural....	515	57,740	531	63,216	521	67,808	514	81,090	501	97,065	-13	15,975
Research Management and Support...............	106	7,443	107	7,926	104	8,038	100	7,990	98	8,167	-2	177
Total, Obligations.....	621	90,663	638	97,880	625	102,395	614	116,899	599	135,330	-15	18,431
Unobligated Balance Lapsing...............		225		151		117						
Total, Budget Authority..	621	90,888	638	98,031	625	102,512	614	116,899	599	135,330	-15	18,431

NOTE: Includes 10 FTEs associated with HIV research activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

National Library of Medicine

1993 Actual		1994 Appropriation		1995 Current Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
625	$102,512,000	614	$116,899,000	599	$135,330,000	-15	+$18,431,000

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the National Library of Medicine. Justification of NIH-wide FY 1995 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

The National Library of Medicine is known as one of the world's "highest-tech" libraries. NLM databases are found to be indispensable by health professionals around the world for research, education, and medical practice. The largest and most well-known of the NLM databases is MEDLINE. MEDLINE contains references, many with abstracts, to 7.5 million journal articles from 1966 to the present. This database is available through formal agreements between NLM and foreign institutions, through commercial online vendors and on compact disks produced by private companies. Perhaps the fastest growing means of MEDLINE access is Internet--the nation's evolving information superhighway.

Primarily as a result of the continued popularity of the "Grateful Med" software, the number of users of NLM's online network has climbed to 80,000. Grateful Med permits anyone with a modem-equipped microcomputer to have direct, simple, and inexpensive access to MEDLINE and other NLM databases. Another reason for the dramatic increase in number of users is the general acclaim with which the lowering of access fees by about 40 percent was greeted. This was done in response to a directive from the Congress that NLM not let charges inhibit or discourage online access. The Library has carried this directive a step further in 1994 by offering its three AIDS-related databases and a directory of information sources available free to all users. A substantial portion of the total online usage is attributable to the searching by members of the National Network of Libraries of Medicine (NN/LM) for their patrons. The Network, now comprising 4,000 member institutions, is a vital link between information services pioneered by the NLM and the community of health professionals that depend on them. NN/LM members play an important part in helping NLM reach remote, rural, and otherwise underserved health professionals who can benefit from online access to the biomedical literature.

Outreach to health professionals is a high priority of the NLM. With the *Index Medicus* in 1879, the Library pioneered in providing the medical community with high quality tools for accessing the health science literature. Today, NLM's MEDLINE and other online databases provide an infinitely higher degree of access--easy and economical--to the immense scientific literature of medicine. The challenge now is to ensure that all health professionals, regardless of geographic setting or work environment, have this access.

As an adjunct to the national health care reform effort, the Library is placing great emphasis on that part of the literature dealing specifically with how to improve patient care. A new National Information Center on Health Services Research and Health Care Technology has been established within the National Library of Medicine. It is working to make the results of health services research, including technology assessments and practice guidelines, readily available to doctors, administrators, policy makers, and information professionals. A new online database covering the literature of health services research is now being tested and will soon be ready for general access.

The multi-agency High Performance Computer and Communications (HPCC) initiative has now been integrated into the programs of the Library. The National Coordination Office for HPCC, headed by the NLM director, continues to reside at the Library. NLM projects related to the HPCC initiative fall into several categories: providing grant assistance to connect health institutions to the world of computerized information resources via the Internet, medical imaging, and biotechnology. The Library components primarily responsible for these various HPCC-related programs are the Lister Hill National Center for Biomedical Communications and the National Center for Biotechnology Information.

In addition to continuing its program of grant support to assist hospitals and other institutions to link up to the present Internet, the NLM has funded the first in a series of HPCC health-related applications. A $4.15-million contract is supporting a consortium of West Virginia institutions to install a system that applies advanced networking technologies to delivering health care in both rural and urban areas of the state. The objective is to demonstrate that physicians can treat patients using electronic patient records and information from distributed sites, and that a network of primary care and specialized care providers can collaborate to meet community health needs. The successful outcome of this project will have obvious implications for containing health care costs while raising the quality of patient care. NLM expects to award approximately 10 new awards in FY 1994 primarily supporting testbed networks that link hospitals, clinics, medical schools, medical libraries, and universities to enable health care providers and researchers to share medical data and imaging. This will include collaborative technology to allow real-time treatment to patients in remote locations.

In the area of imaging, NLM's "Visible Human" project is advancing. This is a collaborative program with the academic community to build an immense digital image library representing x-y-z numerical coordinates of the male and female human body. The first phase, to acquire such data from photographic, computed tomography, and magnetic resonance imaging, is now under way and the resulting data will be made available. This project promises to provide an unprecedented image resource for use in medical education and in developing computer graphics tools for computer-aided surgical planning and radiologic interpretation. The National Center for Biotechnology Information assumed responsibility for the GenBank DNA Sequence Database in 1992. The Center has been successful in expanding the scope of the database and the forms in which it is available. Some 3 million searches a year are now being done on GenBank--both online and on compact disk. The Center's scientists also perform research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules and compounds. These methods are widely published and made available to scientists around the world.

The President's appropriation request of $135,330,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the National Library of Medicine during the last five years has been as follows:

Year	Amount	FTE
FY 1990	$85,235,000	586
FY 1991	90,888,000	621
FY 1992	98,031,000	638
FY 1993	102,512,000	625
FY 1994	116,899,000	614

Purpose and Method of Operation

To maintain information services in support of research, health care delivery, and education, the Library's programs are conducted and supported through the following activities: extramural programs, intramural programs, and research management and support. The primary goal of these activities is to ensure maximum application of biomedical knowledge and state-of-the-art health care improvements resulting from advances in biomedical research.

Overall Budget Policy

The FY 1995 budget request for the National Library of Medicine is $135,330,000, an increase of $18,431,000 over the comparable FY 1994 level of $116,899,000. The request includes support for 599 FTEs. The request continues to emphasize support for library operations including literature acquisition, management, dissemination, and preservation, and for grants in Integrated Advanced Information Management Systems, training, medical informatics, biotechnology and other research and development activities.

The request includes $38,200,000 for High Performance Computing and Communications; an increase of $12,000,000 over the FY 1994. This level will permit NLM to institute new programs and enhance existing programs in connectivity, visualization, and database technology that will have profound impact on medical practice, research, and education.

For extramural programs, the FY 1995 request is $30,098,000; an increase of $2,279,000 over the FY 1994 comparable level. The request will support a total of 111 awards. For biotechnology information activities, this request includes support for 13 grants, as compared to 12 in FY 1994. For IAIMS, this includes funding for three Phase II noncompeting awards. Three Phase I and two Phase II competing awards will be made. For intramural programs, the FY 1995 request is $97,065,000; an increase of $15,975,000 over the FY 1994 comparable level. For research management and support activities, the FY 1995 request is $8,167,000; an increase of $177,000 over the FY 1994 level. The increase will provide for services provided centrally, built-in increases for personnel and basic program requirements.

Funding for the National Center for Biotechnology Information is $10,354,000 at the FY 1995 request level, compared to $10,066,000 in FY 1994, an increase of $288,000. The remaining resources will support the continuation of projects that are key to the development of improved and enhanced biotechnology information services. The FY 1994 administrative cost estimate for the NLM will be changed to reflect a technical/adjustment. The FY 1994 current estimate is $80,283,000, a decrease of $11,268,000 from the amount specified in the FY 1994 appropriation bill.

National Library of Medicine

Extramural Activities

1995 Authorizing Legislation - Section 301, 465-467, and 469-477 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$26,552,000	$27,819,000	$30,098,000	+$2,279,000

The NLM's Extramural Programs Division provides a range of grants relating to the management, dissemination, and use of medical knowledge. Authorized by Public Health Service laws including the Medical Library Assistance Act (MLAA). These grants seek to improve biomedical communication and knowledge access and represent the only Federal programs focusing on information issues that concern the entire health community.

The President's appropriation request of $30,098,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the Extramural Programs during the last five years has been as follows:

FY 1990	$23,618,000
FY 1991	25,491,000
FY 1992	26,741,000
FY 1993	26,552,000
FY 1994	27,819,000

Rationale for Budget Request

The FY 1995 budget request for NLM's Extramural Programs is $30,098,000 which will support approximately 111 awards. This represents an increase of $2,279,000 and a decrease of three awards from the FY 1994 estimate. With the FY 1995 extramural request these funds will provide support for the following activities: Medical Library Assistance, $16,622,000, an increase of $939,000 or six percent over the FY 1994 estimate of $15,683,000; PHS 301, $13,476,000, an increase of $1,340,000 or 11 percent over the FY 1994 estimate of $12,136,000.

Medical Library Assistance Programs

Integrated Academic Information Management System (IAIMS) Program--The IAIMS initiative is designed to create model computerized information systems to serve health professionals in complex academic health centers. Currently each institution has a host of separate databases with little connection among them. IAIMS fosters integration such that from a desk top terminal, the user can gain rapid access to various institutional databases: e.g., patient records, laboratory tests and results, previous treatment protocols, pertinent bibliographic databases, remote files--such as a tumor registry in another state--administrative data, and clinical decision-making systems. "One-stop information shopping" could be on all appropriate desk tops.

NLM provides support to assist in the planning, development, and implementation of IAIMS. There are now five institutions which have successfully competed for the third and final implementation phase of this program.

To meet changing national needs, IAIMS was significantly revised in 1992 to shorten the development time, and to place greater emphasis on clinical elements such as quality control and outcome analysis, and on connections to national information networks. NLM plans to have five new operational grants by end of FY 1995.

Medical Library Resource Grants--Resource Grants assist health science libraries to improve information services to health personnel engaged in education, research and patient care. Present emphasis for the resource grants is on facilitating connection to national databases by networks for both health professionals and librarians. As the new technology penetrates the workplace, biomedical information will more and more be seen as a vast national library, composed of a myriad of local collections which are available to all through computers and telecommunications. This program offers two types of grants: Information Access Grants and Information Systems Grants.

The Information Access Grant is directed towards the libraries of small and medium-size hospitals and similar health-related institutions, and promotes access to information resources via new technologies. The Information Systems Grant, which also emphasizes computer and telecommunications technologies, is directed towards larger hospitals and academic health centers, and encourages networking, connectivity and systems integration. This program will be continued and expanded in 1995 because of the marked increase in applications now being received.

Research Grants in Medical Librarianship and Medical Information Science --NLM offers assistance for research and career development opportunities in Health Science Librarianship and Information Science. Investigations in this program area include evaluation of managerial and organization structure for improved information service, studies of how health information professionals perceive their information requirements, and how medical institutions can utilize new technologies for higher levels of information access. The program is expected to receive increased emphasis in FY 1995 in association with NLM's current planning panel on educational needs of the librarian of the future.

Training in Medical Informatics and Biotechnology Information--NLM is the prime supporter, nationally, of university programs which provide research training in medical informatics, and the related subfield which deals with biotechnology and molecular biology. Such programs are designed to train investigators who are well-equipped to address fundamental issues in the management of health knowledge. Trainees in this program will contribute to the growth of information sciences by analyzing special structures for managing this knowledge and will enable biomedicine to take advantage of the enormous capabilities of computer science for organizing, retrieving, and utilizing health knowledge. To fill an urgent need for informatics professionals able to bring the results of research to practical fruition, NLM announced in late 1991 the creation of a new fellowship in applied informatics, which will provide up to three years of training for those interested in learning some aspect of informatics which can then be applied to their primary discipline. IAIMS, newer library methods, computerized patient records, informatics aspects of radiotherapy, dentistry, and nursing, artificial intelligence programs, and medical education are among the areas which may be studied by such fellows. The institutional training program will reach its steady state in FY 1995 with about 120 fellows enrolled nationally. The fellowship in applied informatics has been particularly popular and will be significantly increased in FY 1995 because of the importance of such trained personnel in developing the new electronic information systems within our health institutions.

High Performance Computing and Communications (HPCC)--In consonance with this initiative, Extramural Programs (EP) again offered the program initiated in 1992, and awarded a number of grants to connect medical institutions to the high-speed network. Working in collaboration with the Connections Program of the National Science Foundation, EP provided grant funds for Internet connections to 16 health institutions in FY 1993, and expects to continue annual increases for this vital assistance to the infrastructure which must be put in place if the information superhighway is to be a reality. FY 1995 target is about 25 new institutions.

EP will continue support for demonstration grants designed to illustrate utility and feasibility of HPCC for biomedicine at Missouri (use of supercomputers in genome research), North Carolina (use of supercomputers in radiation treatment of brain tumors), and Michigan (creation of a national databank for confocal microscopy images), all of which will be completed in FY 1995.

An important new program was launched in FY 1994 through a Cooperative Agreement granting program in the general area of the Electronic Medical Record System. NLM agrees with the widely-held belief that a nation-wide digital information base for documenting patient care is essential to health care reform, and modern health care management. A practical computerized patient record system remains to be developed if a national clinical database is to be achieved. The NLM will be joined by the Agency for Health Care Policy and Research in sponsoring the Cooperative Agreement. Funds for the program in FY 1994 will derive from Health Services Research sources, but there is no question that this area of research and development is a key item in HPCC, and has been so identified by the Congress. By FY 1995 the awards will have been made and the work well begun. Because of the central importance of electronic health records to health care reform, this grant program will have extremely high priority in the FY 1995 budget for expansion.

Outreach Initiative--NLM continues to build upon and enhance existing outreach activities to improve access by health professionals to NLM's information resources. The focus of these activities has been enhancing the National Network of Libraries of Medicine (NN/LM) and improving access by individual health professionals to NLM's information products and services, especially by persons presently unaffiliated with an institution and/or who are located in rural or other medically underserved settings.

Through the addition of special enhancements to the existing (NN/LM) contracts, the NLM has funded demonstration projects in twelve states to test varying means of increasing awareness of and access to NLM's information products and services. Another program, which was recently developed provides for small competitive contracts awarded directly by NLM to network libraries for the purpose of introducing online searching via GRATEFUL MED to health professionals in rural and inner city areas. All of these outreach efforts are aimed at linking underserved health professionals to the National Network; however, they should also encourage the NN/LM and network member libraries to become more active partners with NLM in its outreach program.

In training, the newly established Fellowships in Applied Informatics have as one goal the training of professionals from underserved areas who can then return to their home institutions with the expertise needed to develop and implement modern biomedical information systems.

Almost all of the Information Access grants, and many of the Information Systems grants involve rural or inner city institutions. For FY 1995 NLM expects to place increased emphasis on the inner cities, which have so far received less support than rural areas, and may need some additional NLM effort to inform potential candidates about the program.

Publications--The Publication program is small but vital because few alternate sources of support are available. This program provides small grants to scholars, primarily in the field of history of medicine and science, who seek partial support while preparing a manuscript for publication.

PHS 301 Programs

Medical Informatics Research--Through the medical informatics program, NLM supports work on fundamental knowledge issues. These concern the extraction, organization, retrieval, and utilization of knowledge, involving methodologies such as artificial intelligence, computer sciences, computational linguistics, medical decision sciences, cognitive psychology, and related information-oriented fields. Funds in FY 1995 will probably permit funding of only approximately six new grants in this area. NLM expects to see particular emphasis on expert systems to assist medical decision making, and telemedicine.

Biotechnology Information Research--In the area of biotechnology information, extramural research is supported to investigate effective methodologies of reorganizing and analyzing data relating to molecular control of life processes. Relevant problems include designing and managing databases, retrieving information from multiple factual databases, and pattern-matching algorithms for biological sequences. Scientific advances in molecular biology will depend in large part on successful resolution of knowledge and information issues. Grants in this area will increase because of an expected transfer within NLM. In addition, NLM expects to focus more support on vital national databases in protein structure and function which can serve as a national resource for investigators in this field. For FY 1995 NLM has particular interest in genome sequency databases, and in image databases which capture the physical structure of these genetic molecules.

National Library of Medicine

Intramural Activities

1995 Authorizing Legislation - Section 301, 465-467, and 478 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
521	$67,865,000	514	$81,090,000	501	$97,065,000	-13	+$15,975,000

NLM's intramural activities are carried out by four major components: Library Operations acquires and preserves library materials pertinent to medicine; organizes these materials by cataloging, indexing and bibliographical listing; disseminates its authoritative indexing and cataloging records in publications, online files, and other machine-readable forms; lends originals or photocopies of documents from NLM's comprehensive collection; provides reference and research assistance as a back-up to services available from the National Network of Libraries of Medicine; and develops and enhances information services in the field of health services research.

The Lister Hill National Center for Biomedical Communications explores the use of computer, communication, and audiovisual technologies for improving the organization, dissemination, and utilization of biomedical information. The National Center for Biotechnology Information performs basic and applied research using mathematical and computational approaches; collects and organizes molecular sequences data; develops software tools for analyzing and accessing data; and distributes data through high-speed network-based systems and other electronic media.

The Specialized Information Services (SIS) manages the Toxicology Information Program (TIP) and develops computerized databases in pharmacology, toxicology, and environmental sciences. They include data related to long-term, low-level exposure to hazardous substances, and on the health effects induced by chemical carcinogenesis, teratogenesis, and mutagenesis. TIP is one of the Nation's most important sources of information for emergency response to toxic chemical spills and the release of other health and environmental or occupational hazards.

The President's appropriation request of $97,065,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the Intramural Programs during the last five years has been as follows:

Year	Amount	FTE
FY 1990	$54,677,000	482
FY 1991	57,954,000	515
FY 1992	63,326,000	531
FY 1993	67,865,000	521
FY 1994	81,090,000	514

Rationale for the Budget Request

The FY 1995 budget request for Intramural Programs is $97,065,000. This is an increase of $15,975,000 over FY 1994 and will provide increased funding for the high performance computing and communications initiative. The FY 1994 administrative cost estimate for the NLM will be changed to reflect a technical/adjustment. The FY 1994 current estimate is $51,293,000, a decrease of $41,291,000 from the amount specified in the FY 1994 appropriation bill.

Library Operations

NLM's basic mission is to collect, organize, and provide access to the world's biomedical literature in support of the progress of medicine and the improvement of public health. Library Operations acquires and preserves the biomedical literature; organizes this literature through authoritative cataloging and indexing; disseminates NLM bibliographical records in publications, online files, and other machine-readable forms; lends or copies documents in the NLM collection as a back-up to document delivery service provided by other U.S. biomedical libraries; provides reference and research assistance to health professionals; and maintains an active program of scholarship in the history of medicine. Library Operations also directs the National Network of Libraries of Medicine or NN/LM and cooperates with the Library of Congress and the National Agricultural Library to enhance the general level of library service available in the United States.

Acquisition--NLM is the largest biomedical library in the world, with a collection of 4.9 million items including books, journal volumes, theses, pamphlets, audiovisuals, computer software, microforms, pictures, and manuscripts. To maintain and enhance this comprehensive collection, in FY 1995 the Library will continue to purchase the world's biomedical literature in an increasing variety of formats. The cost of biomedical literature invariably increases at a rate that far exceeds general inflation and is particularly vulnerable to fluctuations in currency exchange rates.

Collection Preservation and Maintenance--NLM works to ensure the long-term availability of the scholarly record of biomedicine by preserving endangered items in its collection and promoting the use of more permanent materials in new biomedical publications. In FY 1995, the Library will use contract assistance to bind more than 25,000 volumes, microfilm about 5,000 brittle books and journal volumes, and conserve several hundred rare or unique items from its rare book, manuscript, picture, and audiovisual collections.

Creation of Bibliographic Data--One of NLM's most important activities is the creation of the authoritative indexing and cataloging records for the biomedical literature that provide an essential foundation for the Library's online retrieval, publication, reference and document delivery services. In FY 1995, NLM expects to index about 400,000 articles and to catalog 23,000 books, serials, audiovisuals, computer software packages, etc., with the assistance of contracts, interagency agreements, and International MEDLARS Centers. NLM will begin to index an additional 100 journals and will review its existing coverage of several specific subject areas. An NIH-chartered committee of outside experts, the Literature Selection Technical Review Committee, advises the Library on which journals should be indexed for MEDLINE and Index Medicus. Work will continue on enhancing and upgrading the computer software and hardware that support indexing and cataloging, including a major project to implement a more flexible and less redundant approach to building, storing, and updating NLM's massive databases of indexed citations.

Dissemination of Bibliographic Data--NLM's authoritative bibliographic data are distributed online, in various machine-readable formats, and in a series of publications including Index Medicus, NLM's major index to about 3,000 biomedical periodicals. In FY 1995, NLM will continue to expand the electronic dissemination of its data via the Internet and to phase out selected printed publications that have outlived their usefulness.

NLM has over 75,000 online users and this number is expected to continue to increase at the rate of at least 15-25 percent per year, due to a combination of outreach efforts, increased flat-rate pricing options, and improvements in the range of information offered and in online access mechanisms such as Grateful Med. In addition to new AIDS and Health Services Research information, by FY 1995 NLM should have expanded coverage of ongoing clinical trials (as a result of collaboration with the NIH Offices of the Medical Applications of Research and Research in Women's Health), space life sciences (in cooperation with NASA), and health education materials produced by NIH Institutes and other Federal agencies including the CDC. In 1995, the Library will implement key segments of its plan to move to a more flexible, open system architecture which will support better access to NLM data from external systems connected via the National Information Infrastructure and provide a range of automated search assistance to individual users. This work, in combination with the Unified Medical Language System Project, will enable effective connections between computer-based patient records systems and NLM databases that can assist in improving patient care decisions.

Reference Services and Document Delivery--NLM provides reference service and document delivery as a national back-up to services available from the more than 4,000 members of the National Network of Libraries of Medicine, as well as serving onsite users of NLM's collection. The Library expects to respond to more than 71,000 reference requests and to process at least 550,000 document requests in FY 1995. By that time the number of health sciences libraries using DOCLINE, NLM's automated request and routing system, is likely to be 3,000 and the system should be handling an annual volume of more than 3 million document requests, including many automatically referred by individual health professionals who use the Loansome Doc feature of Grateful Med. An increasing, although probably still relatively small, percentage of these requests will be filled by transmission of electronic page images via the Internet. To handle this mode of distribution, NLM and network libraries will need to upgrade their equipment and more institutions will need high speed connections to the Internet.

Health Services Research--The 1993 NIH Revitalization Act created a new National Information Center on Health Services Research and Health Care Technology to improve "... the collection, storage, analysis, retrieval, and dissemination of information on health services research, clinical practice guidelines, and on health care technology, including the assessment of such technology." In FY 1994, the NLM budget was increased by $8 million to fund the Center's activities, a very substantial increment in the resources available to NLM for health services research information services.

The new Center replaced and expanded upon NLM's existing Office of Health Services Research Information, which was established in 1990. HSTAR (Health Services/Technology Assessment Research), a new bibliographic database covering journal articles, books, technical reports, government documents, etc. became available to NLM's users in January 1994. In FY 1995, NLM will have expanded its array of health services research databases to include full-text online access to AHCPR guidelines and NIH Consensus Development statements, a health services research-in-progress database, and a directory of datasets useful to health services researchers. NLM will also be conducting an expanded program of training and outreach for medical librarians so they can respond more effectively to health services research, policy, and planning inquiries and for individual health professionals, researchers, administrators, planners, etc. so they can make more effective use of available information services.

The development of computer-based patient record systems will allow extensive health services research data to be produced as a by-product of current health care. To foster the development of such systems, NLM collaborates with the Agency for Health Care Policy and Research to fund research and demonstration sites to test emerging national standards for patient records; to apply NLM's UMLS Knowledge Sources to the problem of linking individual patient records to relevant information in practice guidelines, expert systems, and bibliographic and factual databases such as those created by NLM; and to develop workable strategies for abstracting useful health services research data from patient records to relevant information in practice guidelines, expert systems, and bibliographic and factual databases such as those created by NLM; and to develop workable strategies for abstracting useful health services research data from patient record systems while safeguarding patient privacy.

Lister Hill National Center for Biomedical Communications

The Lister Hill National Center for Biomedical Communications (LHNCBC) is a research and development division of the National Library of Medicine which assists the Library and its health informatics constituents in using advanced computer and communications technologies. LHNCBC programs create new ways for acquiring, storing, retrieving, analyzing, communicating, and presenting the knowledge of human medicine in computerized form. This knowledge includes the text of journal articles, facts from databases, digital images, and the representation of human problem-solving expertise. Research projects conducted and supported by the Center include applications of computer technology as varied as the development of natural language understanding programs to enable computers to "read" and translate biomedical literature, to the display and analysis of three dimensional electronic images of human anatomy for more accurate instruction of health professions students. LHNCBC will initiate or extend several major program efforts:

Three Dimensional Anatomic Imaging. The Center will continue work on its "Visible Human" project to construct a digital library representing complete human beings at millimeter level resolution. The long term goal of the project is to produce a system allowing one to search for pictures using words and concepts, and for words and concepts using pictures. Currently LHNCBC is developing and implementing plans to distribute the Visible Human data in an electronic publication media, and over the Internet; continuing the design and development phase for a two dimensional database system which underpins the 3-D display graphics. In fiscal year 1995, the Center will extend the image data distribution and test preliminary models of the two dimensional database.

Digital Radiology Images. LHNCBC will implement a system called DXPnet (Diagnostic X-ray Prototype Network) which can store and transmit radiology images over the National Research and Education Network. Networking will permit the use of remote radiological services and will allow collaboration among geographically separated investigators.

High Performance Computing and Communications and Medicine Fellowship Program. This fellowship program will be a special track within NLM's current fellowship programs for Informatics Research and Applied Informatics. Accepted fellows will have the Ph.D. or M.D. degree and participate in LHNCBC research activities at the intersection of high performance computing and communications and medical informatics.

Broad Agency Announcement (BAA). In FY 1994 the LHNCBC continued supporting through a major Broad Agency Announcement collaborative research in biomedical applications of computing and digital communications. As part of the overall NIH HPCC effort, the National Library of Medicine HPCC program seeks to develop and demonstrate the utility of HPCC technologies for health care. The first award was made to West Virginia University Research Foundation for developing and demonstrating how new technologies can provide more diagnostic information to doctors about patient being treated at rural clinics. An additional estimated 10 projects will be supported with emphasis on the establishment of testbed networks for the testing and development of methods supporting improved health care. These projects will continue to be supported and expanded in Fiscal Year 1995 as the published results and applications demonstrated will increase the expertise available within the health care community.

DocView (Document Delivery over Internet). The DocView Program is a prototype for the era of paperless electronic publication. When completed it will allow a remote user to retrieve document images over the Internet, read the images on a workstation in a manner nearly identical to reading the corresponding printed pages, electronically "bookmark" selected pages, manipulate images (zoom, pan, scroll), modify images, cut and paste images, retain selected material in electronic form, and print only if desired.

Unified Medical Language System. NLM's UMLS Project develops, tests, and implements Knowledge Sources and software that help health professionals and researchers to overcome the barriers to effective information retrieval caused by the differences in the vocabularies used in different types of information sources and by the huge number of disparate databases and systems that may have information relevant to a particular question. By 1995, the UMLS Knowledge Sources and associated programs will be accessible to systems developers and other users via the Internet. UMLS products will be assisting users of NLM's own databases to formulate more effective queries and will be selecting the NLM databases most likely to contain information relevant to those queries and will also be used to connect patient records in external systems to relevant NLM information sources. The UMLS Information Sources Map will assist users and computer programs to navigate among the tremendous array of biomedical information sources available via the National Information

Infrastructure. This map will be maintained and updated via the Internet with assistance from the producers of the information sources and members of the National Network of Libraries of Medicine.

National Center for Biotechnology Information

The National Center for Biotechnology Information (NCBI) is responsible for managing and distributing the growing body of information in the field of molecular biology, particularly genetic sequence information. Progress in molecular biology and commercial applications in biotechnology rely on the availability of comprehensive, accurate, and up-to-date sequence databases. NCBI serves the biology and biotechnology community by: (1) performing basic and applied research in biology using mathematical and computational approaches; (2) collecting and organizing information about molecular sequences in the NIH GenBank database; (3) developing new software tools for analyzing and accessing the data; and (4) distributing the data through high-speed network-based systems and other electronic media.

The major database responsibility of the NCBI is GenBank, the NIH database of sequence data. NCBI produces and distributes GenBank, the world's foremost collection of DNA sequence data, with over 150,000 sequences and over 164 million base pairs of data from over 5,000 different species. With the rapid pace in sequencing technology, NCBI must cope with the database's exponential growth: doubling in size every 20 months. GenBank is used by every molecular biology laboratory throughout the world involved in gene sequencing to determine if a sequence is new and what its function may be.

For FY 1995, NCBI will launch a major effort to improve the quality and accuracy of the data through automated software and quality control checks. Since an increasing amount of the data is now derived directly from authors who submit it to the database prior to publication, NCBI is developing a new software system that will allow authors to send their data more conveniently to the database as well as perform essential quality checks and analysis on the sequence data itself. Researchers will be able to prepare a sequence for submission, compare that sequence against a comprehensive database, check it for vector contamination and accuracy of translation quickly and efficiently over the Internet. This will not only facilitate the submission process, but will ensure a more accurate and comprehensive set of sequence data.

A second planned activity is to link all known sequence data from U.S. and foreign sources within a single database system so that researchers can avoid having to locate and search multiple, separate, and often inaccessible sources. NCBI works closely with the academic and commercial laboratories (primarily pharmaceutical firms) to meet their sequence data needs, specifically in the area of rational drug design by linking 3-D structural and sequence information. New and expanded databases of cDNA and sequence tagged site (STS) data will be developed to meet the needs of genome research.

A third activity is to expand the search and retrieval services via the "information superhighway". A rapidly increasing number of scientists are connected to the Internet and routinely use the network to conduct their searches and analyses. Over the past 12 months, for example, NCBI has processed searches from over 17,000 different users. Each day over 5000 queries are handled by NCBI computers with response times measured in seconds.

To accommodate the growth in data and users, NCBI will be developing a new version of the sequence database that will permit searches to be run against a non-redundant and highly informative set of sequences. This will improve both the accuracy and the speed of searching. New datasets will be developed for the network search system, Entrez, to provide researchers with a larger set of Medline records which will be linkable to sequences and the proteins they encode. New software is being developed to take advantage of the performance gains of low-cost, scaleable parallel computers. With these systems, search times of seconds for comparing a new, unknown sequence against several hundred thousand sequences can be achieved.

NCBI will continue to work with other Federal agencies such as the Department of Agriculture and the U.S. Patent and Trademark Office (USPTO) to ensure that sequence data from the Plant Genome Project and in issued patents is included. NCBI collaborates closely with data sources in Europe (European Molecular Biology Laboratory) and in Japan (National Institute of Genetics) to maintain international coverage of gene sequence information.

Finally, NCBI will continue to strengthen its extensive intramural research program in computational molecular biology and play a key role in assisting gene sequencing groups in the analysis and identification of function of newly sequenced DNA and in protein structure prediction. Continued large-scale genome analysis is underway on the organization of RNA viruses, large DNA viruses, and in the integration of genetic and physical map data for the E. coli genome. Collaborations formed earlier during the discovery and analysis of several new human disease genes are continuing as further details emerge on the function of the familial colon cancer gene and Kallmann syndrome gene. Members also work closely with the newly established NIH intramural program in human genome research under Dr. Francis Collins, head of the NIH Human Genome Program.

Toxicology Information Program (TIP)

Specialized Information Services (SIS) manages a national Toxicology Information Program (TIP) and develops computerized databases in pharmacology, toxicology, and environmental sciences. All TIP databases are now available on the INTERNET. Private sector vendors license TIP databases for Online or CD-ROM distribution, thus increasing access to this storehouse of chemical and toxicological information. In FY 1995, NLM will continue supporting and expanding these databases and maintain the same level of collaborative relationships with other federal agencies and the private sector.

The Toxicology Data Network (TOXNET) system and its array of data banks constitute one of the world's most comprehensive sources of information on the health and environmental effects of hazardous substances. In FY 1995, this computer system will continue to offer the following services: Hazardous Substances Data Bank (HSDB) contains data on the toxic and hazardous effects of 4,400 chemicals whose exposure potential is of concern. Coverage of this file, comprehensive across several categories, includes toxicity and biomedical effects, safety and handling, environmental fate/exposure potential, and other related areas. All data are referenced and peer-reviewed by an external group of scientists.

Toxic Chemical Release Inventory (TRI) series of databases contain data collected annually by the EPA on the releases of some 330 chemicals into the environment or transferred to waste sites. An Interagency Agreement has been established between NLM and EPA to make these data available on TOXNET. Starting in 1995, the data collected will also include any pollution prevention activities by the reporting facilities. Integrated Risk Information System (IRIS) is another EPA database that contains health risk and regulatory information for both carcinogens and non-carcinogens.

Additional TOXNET files made available through collaborative agreements with other agencies include: the Chemical Carcinogenesis Research Information System (CCRIS), a data bank containing published test results from carcinogenicity, genotoxicity, and tumor promotion studies; the GENE-TOX file, which contains data on genetic toxicology compiled and reviewed by EPA; the Registry of Toxic Effects of Chemical Substances (RTECS), a data bank containing mostly animal toxicity values for over 122,000 chemicals; Developmental and Reproductive Toxicology (DART), a bibliographic database concerned with agents that cause birth defects and infertility, as well as the effects of neonatal and childhood exposures; the Environmental Mutagen Information Center (EMIC) database which contains citations to the literature on agents that have been tested for genotoxic activity; and TRIFACTS, a companion file to the TRI series of databases that contains supplemental environmental release data and summary information on health and ecological effects, as well as on safety and handling information for workers, public interest groups and community residents.

CHEMLINE (Chemical Dictionary Online) assists the user in searching NLM's bibliographic and data files for chemical and toxicological information. The file contains over 1.1 million records. ChemID (Chemical Identification File) is an Online directory which contains over 267,000 records and provides a link to selected lists of chemicals maintained by key regulatory and scientific organizations. Data from the European Inventory of Existing Chemical Substances (EINECS), are also available. TOXLINE and TOXLIT are "toxicology" bibliographic retrieval services, which contain over 3,500,000 records.

The Directory of Information Resources Online, is NLM's directory of over 14,000 health and biomedical information and service providers. These resources include voluntary organizations, NIH-supported scientific resources available for use by other biomedical researchers, self-help organizations, poison control centers, and Federal health information clearinghouses. The database has recently been expanded to include electronic resources such as databases and bulletin board systems covering all aspects of health including AIDS and environmental health. Information abstracted from DIRLINE was printed in a booklet entitled Health Hotlines. This booklet lists toll-free telephone numbers of health related organizations that provide information or services to the public. A Guide to NIH HIV/AIDS Information Services as also produced. This booklet contains information and contact points for Public Health Service agency sponsored NIH/AIDS information services.

In FY 1995, NLM's Toxicology Information Program will continue training representatives from Historically Black Colleges and Universities/Minority Institutions (HBCUs/MIs) to utilize its toxicological, environmental and hazardous wastes databases as an integral part of training, research, and community outreach within these environments.

National Library of Medicine

Research Management and Support

1995 Authorizing Legislation - Section 301, 465-467 of the Public Health Service Act. 1995 Authorization: Indefinite.

Budget Authority:

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTE	BA	FTE	BA	FTE	BA	FTE	BA
104	$8,095,000	100	$7,990,000	98	$8,167,000	-2	+$177,000

Research Management and Support funds the salaries and expenses of the staff who provide for overall administration and direction of the National Library of Medicine programs, including the extramural grant and contract programs. Among functions carried out in this activity are execution of basic administrative services; contracts processing and management; grants management and the scientific direction of NLM's extramural programs, financial and personnel management; coordination of equal employment opportunity activities; direction of NLM's international programs; public inquiries and management of the Library's publications; and operations research. NLM's planning and evaluation activities are also provided for in this activity.

The President's appropriation request of $8,167,000 for this account represents current law requirements. No proposed law amounts are included. Funding for Research Management and Support during the last five years has been as follows:

Year	Amount	FTE
FY 1990	$6,940,000	104
FY 1991	7,443,000	106
FY 1992	7,964,000	107
FY 1993	8,095,000	104
FY 1994	7,990,000	100

Rationale for Budget Request

The FY 1995 budget request for Research Management and Support is $8,167,000 and represents an increase of $177,000 above the FY 1994 appropriation. Through this activity, NLM will continue to provide efficient and effective administrative support and management, and scientific direction for its programs. The FY 1994 administrative cost estimate for the NLM will be change to reflect a technical/adjustment. The FY 1994 current estimate is $51,293,000, a decrease of $41,291,000 from the amount specified in the FY 1994 appropriation bill.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Current Estimate	1995 Estimate
Library Operations...............	360	356	347
Lister Hill Center..............	86	85	83
Biotechnology Center............	37	36	35
Toxicology Information..........	38	37	36
Research Management and Support..	104	100	98
Total..........................	625	614	599

Average GS/GM Grade

1990...	GS-11.0
1991...	GS-11.0
1992...	GS-11.0
1993...	GS-11.0
1994...	GS-11.0
1995...	GS-11.0

Note: Includes 10 FTEs associated with HIV Research Activities. These FTEs are included in the NIH Office of AIDS Research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

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NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

For the study of, construction of, and acquisition of equipment for, facilities of or used by the National Institutes of Health, including the acquisition of real property, [$111,039,000] *$113,539,000*, to remain available until expended. (Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1994.)

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation [1]

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation............	$109,608,000	$111,039,000	$113,539,000
Section 511 reduction.....	-877,000	---	---
Subtotal, adjusted appropriation.........	108,731,000	111,039,000	113,539,000
Unobligated balance, start of year...........	199,196,000	198,949,000	---
Unobligated balance, end of year.............	-198,949,000	---	---
Total obligations....	108,978,000	309,988,000	113,539,000

[1] Excludes the following amount for reimbursable activities carried out under this account: FY 1993 -- $13,323,000.

Buildings and Facilities

Summary of Changes

1994 Estimated budget authority	$111,039,000
1995 Estimated budget authority	113,539,000
Net change	+$2,500,000

	Change from Base Budget Authority
Increases:	
A. Program:	
1. Safety and Reliability Upgrades, RML	+$1,000,000
2. Medical Pathological Waste Management System	+3,500,000
3. Clinical Center Review	+2,500,000
4. William H. Natcher Building	+3,300,000
Total increases	+10,300,000
Decreases:	
A. Program:	
1. Clinical Center Essential Maintenance & Safety	-$900,000
2. Infrastructure Modernization Program	-46,000
3. Repairs and Improvements	-1,054,000
4. NIEHS Additions to Facilities	-2,000,000
5. Cell Biology Facility	-3,800,000
Total decreases	-7,800,000
Total, Net Change	+$2,500,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Other services......................	$111,039,000	$113,539,000	+$2,500,000
(Obligations).......................	(309,988,000)	(113,539,000)	(-196,449,000)
Total budget authority by object.....	111,039,000	113,539,000	+2,500,000
(Total obligations by object)........	(309,988,000)	(113,539,000)	(-196,449,000)

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Funded Authorizations:						
Buildings and Facilities............	Title IV, Section 402(b)	40§282	Indefinite	$111,039,000	Indefinite	$113,539,000
Total Budget Authority..				111,039,000		113,539,000

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1986	$14,900,000	$14,900,000	$14,900,000	$14,900,000
1986 Sequester				-641,000
1987	8,000,000	31,900,000	31,900,000	31,900,000
1988	5,000,000	30,000,000	50,000,000	47,870,000
1989	5,000,000	20,000,000	12,500,000	38,532,000
1990	21,600,000	81,600,000	41,600,000	61,600,000
1990 Sequester				-558,000
1991	86,903,000	239,903,000	68,803,000	168,687,000 2/
1991 Sequester				-2,000
1992	104,125,000	108,625,000	89,485,000	103,840,000
1993	72,518,000	70,090,000	59,222,000	108,731,000
1994	108,731,000	114,385,000	101,000,000	111,039,000
1995	113,539,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes enacted administrative reduction of $4,166,000.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Budget Authority by Project
(Dollars in thousands)

	1993 Actual	1994 Appropriation	1995 Estimate	Change
Clinical Center Essential Maintenance and Safety Program	$7,400	$20,900	$20,000	-$900
Infrastructure Modernization Program	35,533	13,485	13,439	-46
Power Plant Safety Program	0	2,000	2,000	0
Asbestos Abatement Program	0	5,500	5,500	0
Fire Protection and Life Safety Program	0	2,000	2,000	0
Safety and Reliability Upgrades, RML	0	1,000	2,000	+1,000
Medical Pathological Waste Management System	0	0	3,500	+3,500
Clinical Center Review	0	0	2,500	+2,500
William H. Natcher Building	29,760	27,500	30,800	+3,300
Turner Construction Claims, North Carolina	5,000	5,000	5,000	0
Repairs and Improvements	10,618	17,854	16,800	-1,054
NIEHS Additions to Facilities	9,920	12,000	10,000	-2,000
Cell Biology Facility	0	3,800	0	-3,800
Intramural Animal Facilities	10,500	0	0	0
Total budget authority	108,731	111,039	113,539	+2,500
Unobligated balance, start of year	199,196	198,949	---	-198,949
Unobligated balance, end of year	-198,949	---	---	---
Total obligations	108,978	309,988	113,539	-196,449

Justification

Buildings and Facilities

	1993 Actual	1994 Appropriation	1995 Estimate	Increase or Decrease
Total budget authority..	$108,731,000	$111,039,000	$113,539,000	+$2,500,000
Total obligations.......	(108,978,000)	(309,988,000)	(113,539,000)	(-196,449,000)

General Statement

This appropriation provides for the design, construction, improvement, and major repair of clinical and laboratory buildings and supporting facilities essential to the mission of the National Institutes of Health. Funds are provided for non-recurring direct construction projects as well as ongoing major repairs and improvements. All funds are available until expended.

Construction of facilities for the National Institutes of Health spans a period of nearly 58 years, dating back to legislation that authorized Building 1 in June 1936. Facilities funded under this appropriation include those required for both research programs and support services at the main NIH Reservation in Bethesda, Maryland, totaling 77 buildings and more than seven million gross square feet of space. Additional facilities are the Frederick Cancer Research and Development Center, Frederick, Maryland; the National Institute of Environmental Health Sciences (NIEHS) facility in Research Triangle Park, North Carolina; the Gerontology Research Center, Baltimore, Maryland; the NIH Animal Center located in Poolesville, Maryland; the Rocky Mountain Laboratory, Hamilton, Montana; and Primate Facilities at Perrine, Florida, New Iberia, Louisiana, and Sabana Seca, Puerto Rico.

The NIH is developing updated master plans scheduled for completion in FY 1994, for both the Bethesda campus and the NIH Animal Center in Poolesville. Significant growth on and off the NIH sites, the aging of the facilities and infrastructure, and the growth of new technologies and the biomedical research programs at NIH have rendered the existing plans of more than two decades nearly obsolete. The new comprehensive master plans will identify programmatic requirements in terms of personnel and physical facilities; establish concepts for future development and land use, buildings, utilities, open space, circulation and traffic management at both sites for the next twenty years; and illustrate how needs for research, clinical, administrative, and support space can be achieved.

The NIH is contending with an aging, deficient physical plant. The majority of our infrastructure systems are between 20 to 40 years old, undersized, and beyond their design life. While we have taken action to minimize the risk of imminent collapse, failure of one or more central systems would mean closure of significant elements of our research program for extended periods of time. To address these deficiencies and plan for the future, the NIH is integrating all corrective and new construction programs into a comprehensive Facilities Revitalization Program. The intent of this program is to develop a long-term strategy to coordinate programs and set priorities so that ongoing laboratory and clinical research as well as anticipated growth can be supported in accordance with modern standards.

Equally, the NIH gives a high priority to safety and health requirements necessary to meet critical infrastructure, occupational, and environmental upgrades to existing NIH facilities in order to protect and support ongoing research programs, including the safety and health of NIH employees and patients. This is the purpose of the Essential Safety and Health Improvement initiative. If the NIH intramural research program is to remain at the forefront of biomedical and health research, our facilities and supporting utilities must be modernized and improved to meet safety and health requirements in order to provide the infrastructure necessary to support the NIH research mission.

The President's Appropriation request of $113,539,000 for this account represents current law requirements. No proposed law amounts are included.

Purpose and Method of Operation

Funding for Buildings and Facilities during the last 5 years has been as follows:

Year	Amount
FY 1990	$46,473,000
FY 1991	167,341,000
FY 1992	101,840,000
FY 1993	108,731,000
FY 1994	111,039,000

The Buildings and Facilities appropriation funds two major requirements of the NIH biomedical research mission: the design and construction of new facilities for NIH research programs and the continuing renovation, alteration, and repair of existing facilities. Long-term projects currently under construction include campus infrastructure modernization, modernization/safety upgrades of the NIH Clinical Center, rehabilitation of the campus' oldest laboratory buildings, the asbestos abatement program, renovation of existing animal facilities, and Phase I of the William H. Natcher Building. Initial construction for replacement of leased facilities at the National Institute of Environmental Health Sciences began in December 1992.

Overall Budget Policy

The 1995 budget request of $113,539,000 reflects the high priority placed on safety and health requirements necessary to meet critical infrastructure and environmental improvements to the existing facilities to protect and support ongoing research programs. The enhanced program for essential safety and health improvements includes funding for the upgrade or replacement of essential equipment and systems to keep the Clinical Center safely operational; the site infrastructure modernization program; the continuation of programs for power plant safety, asbestos abatement, fire protection and life safety, and safety and reliability upgrades at the Rocky Mountain Laboratory; and a replacement Medical Pathological Waste management and disposal system. Funds are included for the development of a set of options relative to the future of the Clinical Center. The request also provides for continued funding for the William H. Natcher Building and replacement facilities at the NIEHS, the third annual payment related to the Turner Construction Company claim settlement, and funding for ongoing repair and improvement of facilities.

Buildings and Facilities

Program Activities

Authorizing Legislation - Section 402(b) of the Public Health Service Act, 1995 Authorization: Indefinite.

Budget Authority:

1993 Actual	1994 Appropriation	1995 Estimate	Increase or Decrease
$108,731,000	$111,039,000	$113,539,000	+$2,500,000

Rationale for the Budget Request

The FY 1995 budget request for Buildings and Facilities is $113,539,000, an increase of $2,500,000 over FY 1994. The basic thrust of the 1995 budget request is the program of essential safety and health improvements required to meet critical infrastructure and environmental improvements to existing NIH facilities in order to protect and support ongoing research programs.

Clinical Center Essential Maintenance and Safety Program

FY 1995 Budget Request.. $20,000,000

The Clinical Center Essential Maintenance and Safety (EMS) Program will rebuild or replace existing systems to provide the minimum improvements necessary to keep the Clinical Center safely operational. Extensive alterations are necessary to comply with safety requirements and allow modern procedures, equipment, and facilities to provide quality patient care and supporting research. The EMS Program will focus on safety issues, hospital accreditation, and major central system renovations to enhance reliability of a facility over 40 years old.

This request is the second year of a four-year program and will provide completion of penthouse enclosures and associated mechanical and electrical systems. Also included in this request is continued design for the next phase of construction. Future requests will provide for the connection of new penthouse equipment to distribution systems, replacement of terminal induction units, and replacement of mechanical equipment located in distributed mechanical rooms.

Infrastructure Modernization Program

FY 1995 Budget Request.. $13,439,000

This request is the fifth year of the nine-year effort for the replacement and expansion of central utility equipment and distribution systems. The majority of the NIH Central Utility Plants and distribution networks are over 40 years old. Obsolescence and system deteriorations due to age, overburdening from growth, and increases in program needs have produced a critical situation where sufficient and uninterrupted services to research and patient care activities can no longer be ensured. The possibility of catastrophic failure has become very real, and the current situation could encumber or destroy the capability to carry out the NIH mission.

To correct this, it is necessary to undergo a programmed restoration, renovation, replacement, and expansion of the mechanical and electrical utility systems, or components thereof. This program is intended to correct safety deficiencies, restore and improve reliability, expand capability, and improve the efficiency of the utility systems. This increment will provide for construction of the east and west tunnels for chilled water and steam and continued funding for inspection.

Power Plant Safety Program

FY 1995 Budget Request... $2,000,000

Recent preliminary studies have identified emissions from the Power Plant to be significantly in excess of National Ambient Air Quality Standards that may adversely impact the occupants within the power plant and surrounding facilities. This is the second year of a five-year program for upgrading the NIH Power Plant, Building 11, to bring emissions in compliance with acceptable air quality standards. This request will initiate the implementation of long-term reduction items, in addition to removal of hazardous materials from within the Power Plant.

Asbestos Abatement Program

FY 1995 Budget Request... $5,500,000

This project provides for the phased removal of asbestos containing materials from various NIH buildings. Insulation, fireproofing, and ceiling and wall finishes containing asbestos are present in virtually all NIH buildings. Disturbed or deteriorating asbestos fibers can be released into the air, risking the health of those persons exposed. Asbestos control practices are instituted whenever there is a risk of exposure to significant airborne asbestos concentrations. This is the second year of a ten-year program.

Fire Protection and Life Safety Program

FY 1995 Budget Request... $2,000,000

Funding is requested for the second year of a multi-year program to upgrade the fire and life safety equipment of NIH buildings on the campus and at the NIH Animal Center. Significant deficiencies exist which compromise NIH's ability to provide adequate protection to all persons using or working in NIH facilities as well as protection of critical research facilities and resources. A master fire protection plan is under development as part of the program. Fire sprinklers and an improved alarm and reporting system will be provided as well as improvements in fire egress.

Safety and Reliability Upgrades, Rocky Mountain Laboratory

FY 1995 Budget Request.. $2,000,000

Funds are requested for the second year of a five-year program for the revitalization of high priority facility reliability and safety upgrades at the Rocky Mountain Laboratory (RML) in Hamilton, Montana. These funds will provide for the upgrade of main distribution systems for supporting fire sprinklers, air conditioning, plumbing, and electrical systems within the RML. In addition, a portion will go toward the demolition and partial upgrade of one of the main laboratory buildings.

Medical Pathological Waste Management System

FY 1995 Budget Request.. $3,500,000

This project provides for the design and implementation of a model Medical Pathological Waste (MPW) management and disposal system to replace existing incinerators located in Building 11. Incinerators 1 and 2 are used in conjunction with the newer incinerator 3 to burn MPW, and their ability to meet future environmental requirements necessitates a program of replacement with a state-of-the-art MPW management and disposal system. A thorough environmental study, including an examination of alternative technologies, will be carried out. The goal is to determine and then implement the safest and most effective system for management and disposal of MPW in terms of meeting the programmatic needs of the NIH biomedical research programs and the best interest of the environment and the health of the community.

Clinical Center Review

FY 1995 Budget Request.. $2,500,000

The FY 1995 request includes funds to further develop a set of options relative to the Clinical Center. The Clinical Center Complex, now with components over 40 years old, is deteriorated, outmoded, and insufficient to support contemporary, high quality biomedical research. Additional information is needed to allow a decision to be made on the best solution to this problem.

As a critical step in the decision-making process, NIH has undertaken a strategic review of the NIH intramural research program to examine the appropriate balance of resources between intramural and extramural research and training. Because of the pivotal role of the NIH Clinical Center in intramural resource usage, and the significant investment that would be required to either replace or restore the existing facility, a decision regarding the future configuration of the Clinical Center Complex should be based on the completion of this review. At that point, a full range of options concerning the Clinical Center will be presented to the Secretary, including a "no-build" option.

William H. Natcher Building

FY 1995 Budget Request.. $30,800,000

The William H. Natcher Building (formerly named the Consolidated Office Building) will consolidate extramural programs currently located on campus and in separate leased off-campus facilities. The building will provide a "Gateway to NIH" image to the campus, house approximately 3,000 personnel, and provide parking for approximately 1,900 cars. The 719,000 gross square foot building will be constructed in two independent phases.

Construction of Phase I (encompassing a conference center) is anticipated for completion in the fall of 1994. Funds previously provided will be used to begin construction of Phase II. This request will be used to continue the funding of construction of Phase II including mechanical, electrical, plumbing and elevator systems. The start of construction of Phase II is dependent on the findings of the Environmental Impact Statement due for completion in February 1994 and other regulatory approvals.

Turner Construction Claims, North Carolina

FY 1995 Budget Request.. $5,000,000

The Department of Health and Human Services awarded a construction contract for the development of the National Institute of Environmental Health Sciences (NIEHS) permanent facilities in the Research Triangle Park, North Carolina, in May 1977. During construction, a number of contractual disputes arose between the Government and Turner Construction Company. These disputes eventually developed into full litigation, and the Armed Services Board of Contract Appeals ruled in favor of the contractor.

All claims against the NIEHS permanent facilities were settled in July 1991. The total claims paid by the Treasury exceeded $25 million. The Department of the Treasury was amenable to NIH's proposal of annual installment payments of $5.0 million per year to the Treasury until the balance is paid. The funds included in this request will support the third payment.

Repairs and Improvements

FY 1995 Budget Request.. $16,800,000

The Repairs and Improvements (R&I) program provides for major repairs and improvements to the physical plants at Bethesda, Poolesville, Baltimore, and Frederick, Maryland; Research Triangle Park, North Carolina; Hamilton, Montana; Perrine, Florida; and other field stations for which NIH has the property-holding responsibility. The costs for some of the projects are recurring and substantial. For example, some projects such as roofs, roads, structures, building and underground utilities require ongoing repairs and maintenance to preserve or achieve reliable and safe conditions. For other projects, the costs are largely one-time, often unpredictable expenditures for major items of equipment requiring emergency repair or replacement such as transformers, chillers, and cooling towers.

In addition, this program supports adjustments to the infrastructure utility systems to provide necessary capacity to accommodate changes in the direction of research. These repairs or replacements require immediate attention, and thus are not suited to a schedule of expenditures such as found in the Infrastructure Modernization Program.

Additions to Program and Support Facilities, NIEHS

FY 1995 Budget Request.. $10,000,000

The FY 1995 request provides for the continuation of two major building additions at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. This will allow for the consolidation of the two NIEHS research and support staffs which are now separated by about one mile. The new additions will enable NIEHS to relocate all programs and activities (except material storage and distribution support) from outmoded, rental facilities into one consolidated laboratory building.

The completed structures will provide major building additions to the existing Building 101. The building additions will include 87,200 net square feet of research program space including magnetic resonance imaging. Office areas will be used for NIEHS extramural and intramural personnel. This increment will allow for the partial completion of the laboratory module including mechanical, electrical, and plumbing utility systems in the interstitial spaces and the penthouses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Office of the Director

FY 1995 Budget

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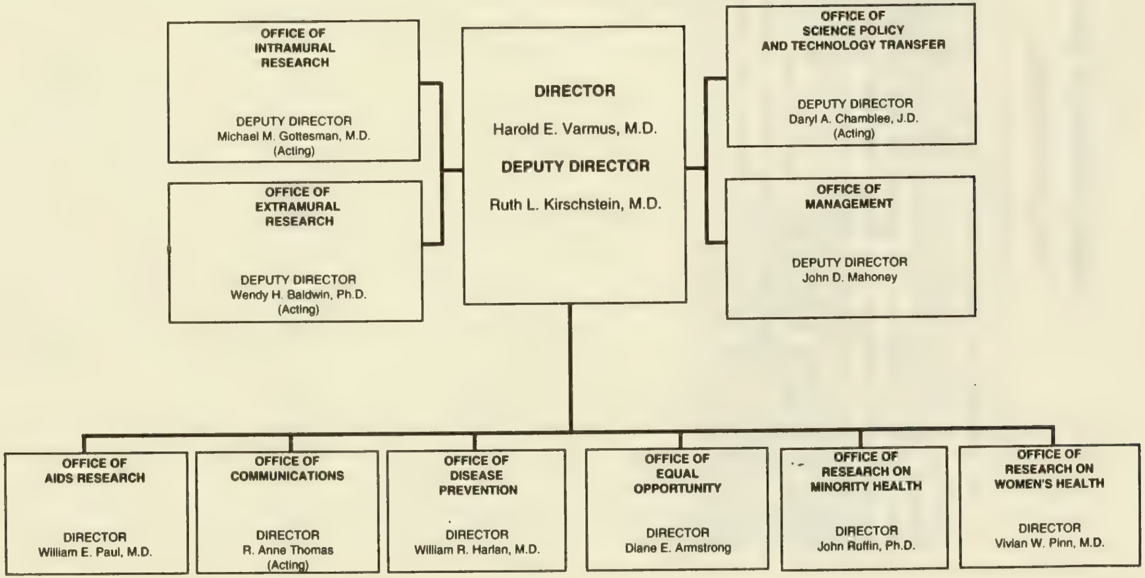
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Office of the Director



NATIONAL INSTITUTES OF HEALTH

Office of the Director

For carrying out the responsibilities of the Office of the Director, National Institutes of Health, [$233,605,000] $233,522,000: *of which $5,200,000 shall not become available for obligation until September 19, 1995:* Provided, that $1,000,000 is for Scholarship and Loan Repayment programs authorized by section 1631 of the Public Health Service Act and shall remain available until September 30, 1996: Provided further, That funding shall be available for the purchase of not to exceed five passenger motor vehicles for replacement only: Provided further, That the Director may direct up to 1 percent of the total amount made available in this Act to all National Institutes of Health appropriations to emergency activities the Director may so designate: Provided further, That no such appropriation shall be increased or decreased by more than 1 percent by any such transfers and that the Congress is promptly notified of the transfer. (Departments of Labor, Health and Human Services and Education, and Related Agencies Appropriations Act, 1994)

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Language Analysis

Language Provision	Explanation
"...of which $5,200,000 shall not become available for obligation until September 19, 1995."	Language has been added to ensure that government-wide outlays limits for domestic discretionary programs established in the Omnibus Budget Reconciliation Act of 1993 (P.L. 103-66) are not exceeded.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation 1/

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation	$192,763,000	$233,605,000	$233,522,000
Section 511 8% reduction	-1,542,000	---	---
Section 216 S&E reduction	-896,000	---	---
Subtotal, adjusted appropriation	190,325,000	233,605,000	233,522,000
Real transfer to other NIH Accounts for Tuberculosis	-187,000	---	---
Comparable transfer to the Office of AIDS Research for HIV activities	-14,757,000	-25,744,000	---
Subtotal, adjusted budget authority	175,381,000	207,861,000	233,522,000
Unobligated balance start of year	1,867,000	---	---
Unobligated balance end of year	---	---	---
Unobligated balance lapsing	-70,000	---	---
Total obligations	177,178,000	207,861,000	233,522,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: FY 1993 - $45,108,000; FY 1994 - $47,291,000; FY 1995 - $47,291,000. The FY 1993 actual, the FY 1994 appropriation and FY 1995 estimate excludes $9,277,000, $9,277,000 and $9,277,000, respectively in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research Management & Support....	716	$175,381,000	717	$207,861,000	704	$233,522,000
OD Operations....................	(658)	(40,825,000)	(658)	(41,865,000)	(643)	(44,626,000)
Director's Discretionary Fund....		(10,329,000)		(7,500,000)		(10,000,000)
Laboratory for Diagnostic Radiology Research............	(9)	(1,908,000)	(9)	(1,948,000)	(9)	(2,053,000)
Extramural Construction..........		(4,949,000)		---		---
Office of Alternative Medicine...	(5)	(1,973,000)	(5)	(3,505,000)	(5)	(3,694,000)
Academic Research Enhancement Award Program.................		(12,861,000)		(13,271,000)		(13,643,000)
Science Education................	(4)	(1,747,000)	(4)	(1,830,000)	(4)	(1,929,000)
Research on Minority Health......	(8)	(9,037,000)	(8)	(9,887,000)	(8)	(10,421,000)
Research on Women's Health.......	(14)	(9,425,000)	(15)	(10,325,000)	(14)	(15,926,000)
Women's Health Initiative........	(16)	(41,559,000)	(16)	(61,252,000)	(16)	(61,252,000)
Minority Health Initiative.......	(2)	(40,768,000)	(2)	(56,478,000)	(2)	(66,478,000)
Loan Repayment Program...........		---		---		(1,000,000)
Office of Behavioral & Social Sciences Research.............		---		---	(3)	(2,500,000)
Total Budget Authority......	716	175,381,000	717	207,861,000	704	233,522,000
Funds reimbursed or directly supporting ICDs................		(127,808,000)		(154,432,000)		(177,506,000)

Note: Includes FTEs associated with NIH Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

DHHS - National Institutes of Health

Office of the Director
Allocation by Mechanism 1/

(Dollars in thousands)

	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
Research Grants:			
Research Projects	$28,349	$35,514	$45,973
Research Centers	---	---	---
Other Research	---	---	---
Total, Res. Grants	$28,349	$35,514	$45,973
Training	21,710	30,387	30,524
R&D Contracts	63,227	90,730	101,730
Intramural Research	8,908	1,948	3,053
Res. Mgmt. and Support	7,413	7,417	7,616
Cancer Control	---	---	---
Construction	4,949	---	---
Total, ICD	134,556	165,996	188,896
OD Operations	40,825	41,865	44,626
Total	175,381	207,861	233,522

1/ This represents a breakout of the OD's budget as it is ultimately expended by mechanism.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Summary of Changes

1994 Estimated budget authority	$207,861,000
1995 Estimated budget authority	233,522,000
Net Change	+25,661,000

	1994 Current Estimate Base		Change from Base	
	(FTEs)	Budget Authority	(FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Annualization of FY 1994 locality pay raise		$38,781,000		+$337,000
2. Within grade increase		38,781,000		+568,000
3. One less day of pay		38,781,000		-149,000
4. FY 1995 Pay Raise		38,781,000		+488,000
5. FECF		20,000,000		+2,000
6. Increased cost of services and supplies		40,315,000		+2,335,000
7. Service and Supply Fund increase		4,480,000		+126,000
8. FTS		216,000		+10,000
Subtotal				+3,717,000
	No.	Amount	No.	Amount
B. Program:				
1. Minority Health Initiative	(2)	56,478,000		+10,000,000
2. Director's Discretionary Fund		7,500,000		+2,500,000
3. Office of Research on Women's Health	(15)	10,325,000		+5,601,000
4. Office of Research on Minority Health	(8)	9,887,000		+534,000
5. Office of Equal Opportunity		1,683,000		+500,000
6. Loan Repayment Program		---		+1,000,000
7. Office of Behavioral & Social Sciences Research		---		+2,500,000
8. FTE Reductions	(717)	41,266,000	(-13)	-691,000
Subtotal			(-13)	+21,944,000
Total Changes			(-13)	+25,661,000

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Full-time equivalent employment.....	717	704	-13
Full-time equivalent of overtime and holiday hours................	5	5	---
Average ES salary..................	$113,654	$115,473	+$1,819
Average GS/GM grade................	10	10	---
Average GS/GM salaries.............	44,785	45,501	+716
Average salary, grades established by act of July 1, 1944 (42 USC 207).....................	76,028	77,244	+1,216
Personnel Compensation:			
Full-time permanent..............	$30,474,000	$30,989,000	+$515,000
Other than full-time permanent....	1,865,000	1,900,000	+35,000
Other personnel compensation......	885,000	906,000	+21,000
Special personnel service payments......................	161,000	166,000	+5,000
Total, personnel compensation...	33,385,000	33,961,000	+576,000
Personnel benefits.................	5,396,000	5,384,000	-12,000
Travel and transportation of persons.........................	304,000	310,000	+6,000
Transportation of things...........	68,000	69,000	+1,000
Rent, communications and utilities..	1,297,000	1,328,000	+31,000
Printing and reproduction..........	602,000	614,000	+12,000

Consultant Services	$3,625,000	$3,696,000	+$71,000
Other services	50,745,000	50,112,000	-633,000
Purchasing from government accts	95,480,000	120,574,000	+25,094,000
Operation of GOCOs	---	---	---
R&D contracts	13,271,000	13,643,000	+372,000
Supplies and materials	732,000	750,000	+18,000
Equipment	2,956,000	3,081,000	+125,000
Total budget authority by object	207,861,000	233,522,000	+25,661,000
Funds reimbursed or directly supporting ICDs	(154,432,000)	(177,506,000)	(+23,074,000)

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Object

	1994 Appropriation	1995 Estimate	Increase or Decrease
Full-time equivalent employment.....	717	704	-13
Full-time equivalent of overtime and holiday hours................	5	5	---
Average ES salary..................	$113,654	$115,473	+$1,819
Average GS/GM grade................	10	10	---
Average GS/GM salaries.............	44,785	45,501	+716
Average salary, grades established by act of July 1, 1944 (42 USC 207)......................	76,028	77,244	+1,216
Personnel Compensation:			
Full-time permanent..............	$30,474,000	$30,989,000	+$515,000
Other than full-time permanent....	1,865,000	1,900,000	+35,000
Other personnel compensation......	885,000	906,000	+21,000
Special personnel service payments......................	161,000	166,000	+5,000
Total, personnel compensation...	33,385,000	33,961,000	+576,000
Personnel benefits.................	5,396,000	5,384,000	-12,000
Travel and transportation of persons..........................	304,000	310,000	+6,000
Transportation of things...........	68,000	69,000	+1,000
Rent, communications and utilities..	1,297,000	1,328,000	+31,000
Printing and reproduction..........	602,000	614,000	+12,000

Consultant Services.................	$3,625,000	$3,696,000	+$71,000
Other services......................	2,865,000	6,102,000	+3,237,000
Purchasing from government accts....	---	---	---
Operation of GOCOs..................	---	---	---
R&D contracts.......................	90,730,000	101,730,000	+11,000,000
Supplies and materials..............	732,000	750,000	+18,000
Equipment...........................	2,956,000	3,081,000	+125,000
Grants, subsides and contributions 1/	65,901,000	76,497,000	+10,596,000
Total budget authority by object.....	207,861,000	233,522,000	+25,661,000
Funds reimbursed or directly supporting ICDs..................	(154,432,000)	(177,506,000)	(+23,074,000)

1/ This represents a breakout of the OD's budget by object class requesting how funds are ultimately expended.

National Institutes of Health
Administrative Costs
Budget Authority
OD

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	30,474	30,474	30,989	515
11.3	Other than full-time permanent	1,865	1,865	1,900	35
11.5	Other personnel compensation	885	885	906	21
11.8	Special personnel services payments	161	161	166	5
11.9	Subtotal, personnel compensation	33,385	33,385	33,961	576
12.1	Civilian personnel benefits	5,396	5,396	5,384	(12)
13.0	Benefits for former personnel	0	0	0	0
	Subtotal Pay Costs	38,781	38,781	39,345	564
21.0	Travel and transportation of persons	304	304	310	6
22.0	Transportation of things	68	68	69	1
23.2	Rental payments to others	0	0	0	0
23.3	Communications, utilities, and miscellaneous charges	1,297	1,297	1,328	31
24.0	Printing and reproduction	602	602	614	12
25.0	Other Services	164,423	6,490	9,798	3,308
26.0	Supplies and materials	732	732	750	18
	Subtotal non-pay costs	167,426	9,493	12,869	3,376
	Total Administrative Costs	206,207	48,274	52,214	3,940

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

Office of the Director

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

Item	
1993 House Report	
Office of Research on Women's Health	
1. The House in its report 103-156, page 71, stated, "The Committee is aware that the nation's science museums have committed to the development of a national public education program on prevention of women's health problems and has increased funding for the Office of Research on Women's Health to begin developing this program".	1. The Office of Research on Women's Health (ORWH) is working with the National Museum of Health and Medicine to develop an exhibit on women's health, as highlighted in the House Report. The exhibit, which should be completed in FY 1995, will enhance public education on the history of research and practice in women's health, and contribute to a greater understanding of women's health issues.
Administrative Costs	
2. The House in its report 103-156, page 71, stated, "In its ongoing effort to contain the growth of the taps on individual Institutes, the Committee directs that spending Management and Service and Supply Funds not exceed the levels proposed in the President's request. If the Department believes it is necessary to increase these funds beyond the permitted levels, it should submit a reprogramming request to the Committee".	2. All Central Service divisions have been provided 1994 funding levels that do not exceed the levels proposed in the President's request for the Management Fund and the Service and Supply Fund.
Osteoporosis	
3. The House in its report 103-156, page 72, stated, "Research on this condition, which is part of the women's health initiative, is conducted at NIH by NIAMS, NIA, NIDDK, and NIDR. The Committee encourages these Institutes to increase funding levels for osteoporosis to build on significant research gains".	3. See National Institute of Arthritis and Musculoskeletal and Skin Disease Senate Report number three.
Diagnostic Radiology	
4. The House in its report 103-156, page 72, stated, "The Committee encourages the laboratory of diagnostic radiology research to further develop those MRI techniques	4. The Laboratory of Diagnostic Radiology Research is developing new techniques for evaluating women who either have early stage breast cancer or are at a high risk of

which hold the greatest promise for detecting breast and ovarian cancer".	developing breast cancer using both Magnetic Resonance Imaging (MRI) and Position Emission Tomography. Research is underway involving the use of MRI to study tumor perfusion in women with early stage breast cancer. In addition, the LDRR is presently building a prototypic Positron Emission Mammography unit which will be used to aid in the localization of small tumors of the breast, and to study changes in tumor metabolism in response to therapy. In addition, LDRR research on tumor markers using monoclonal antibodies tagged with a biocompatible super-paramagnetic magnetoferritins may provide the increased sensitivity to detect early stages of ovarian cancer. Preliminary research using animal models of malignancy is being evaluated.
Minority Appointments 5. The House in its report 103-156, page 72, stated, "Hispanics continue to be seriously underrepresented at all staffing levels at NIH, particularly in high-ranking research and policy positions. The Committee directs NIH to develop a plan for increasing the number of Hispanic personnel at the higher levels and to be prepared to discuss the plan and the schedule for its implementation in hearings on the fiscal year 1995 budget request. The Committee expects the plan to include formal consultation with Hispanic serving institutions and other outside organizations to identify Qualified Hispanic health professionals".	5. The NIH Hispanic Recruitment and Retention Action Plan was established in FY 1992 with a four-year frame to address the critical under-representation of Hispanics at NIH. In addition to this Plan, the NIH Annual Affirmative Employment Program Plan for Minorities and Women includes objectives to increase the applicant pool of Hispanics at all levels.

1993 Senate Report

Medical Research Trust Fund

1. The Senate in its report 103-143, page 77, stated, "The Committee recommends the Secretary give careful consideration to the establishment of a medical research trust fund to augment Federal appropriations for the biomedical enterprise supported by the National Institutes of Health. Mechanisms for generating these funds could take several forms, including a national income tax checkoff of a monthly set-aside from health care premiums".

1. The scientific advances emerging from basic clinical biomedical research contribute significantly toward improving quality of life as well as reducing mortality and morbidity for all Americans. Furthermore, these advances often result in major cost savings in health care expenditures. The goal of identifying alternative sources to augment appropriated funds could be a positive approach to providing support for biomedical research. The Administration is committed to working with Congress to ensure funds are available to support all of the Public Health initiatives. One such approach would be the Medical Research Trust Fund.

Cost Management

2. The Senate in its report 103-143, page 78, stated, "The Committee believes that in order to effectively manage research programs and to assure that maximum benefits are derived from available resources, a certain amount of flexibility must be maintained by the ICDs. The Committee believes a policy which mandates specific increases in average cost of awards from year to year may ultimately restrict or limit their ability to use funds to explore promising areas of research and to take advantage of new or emerging issues based on scientific merit and need. Therefore, the Committee encourages the NIH to review the merits of this plan and to carefully monitor its effect on funding levels to ensure that it does not inappropriately interfere with the overall mission of the individual ICD's by directing them to follow the funding parameters identified in this plan".

2. NIH appreciates the sentiments expressed in the language of the Senate Appropriations Report regarding cost management, specifically the need to the merits of the NIH Financial Management Plan. The NIH Cost Management Committee has, in fact, been reviewing the Plan and its embarking on an approach to developing a revised edition.

Minority Health Initiative

3. The Senate in its report 103-143, page 124, stated, "The Committee urges the Director to utilize a portion of the funds provided to support research into the genes responsible for the onset of diabetes in conjunction with the work underway at the National

3. The ORMH will provide $2,000,000 per year in Fiscal Years 1994, 1995, and 1996 to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to support research into the genes responsible for the onset of diabetes.

Institute of Diabetes and Digestive and Kidney Diseases".

Office of Research on Women's Health

4. The Senate in its report 103-143, page 124, stated, "The Committee urges the NIH to expand support for multidisciplinary, basic research to gain new knowledge into the causes of, and cost-effective therapies for, diseases that affect maturing women. Furthermore, the NIH is encouraged to utilize the resources and experience of institutions devoted solely to women's health issues and located in areas that have a disproportionate share of maturing and elderly women".

4. ORWH is strongly committed to supporting research and activities that will ultimately improve the health of maturing women. The Office is working with several of the NIH Institutes to support research on a wide range of diseases or health concerns of older women. ORWH is currently funding a project to identify abnormal expression of "predisposing genes" for women at risk of developing colon and uterine cancer. Several projects with primary support from NIAMS are ongoing which examine bone disease and bone metabolism. The Office has joined with the National Institute on Aging and the National Institute of Nursing Research (NINR) to cosponsor an RFA on the natural history of menopause. An RFA co-issued with NINR and ACHPR will solicit projects that examine the decision-making process regarding hysterectomy for non-cancerous conditions. We will continue to collaborate on projects among older women and the social roles of older women.

Office of Alternative Medicine

5. The Senate in its report 103-143, page 125, stated, "The Committee directs that the Office of Alternative Medicine continue to perform field investigations for the purpose of preliminary data gathering as well as support clinical investigations of nutritional supplements through the established grant program. The Committee further directs that the NIH continue to provide the highest level of support for the Office to carry out the directives from the Committee".

5. NIH has placed high priority on providing appropriate resources to the Office of Alternative Medicine (OAM) for the purpose of carrying out field investigations so that it may carry out its mission of identifying and evaluating alternative medical practices. Over the past year, OAM has funded several grants that are intended to investigate the role of nutrition and diet, e.g., macrobiotics, on the treatment of cancer. A second area of investigation is the evaluation of multiple antioxidant vitamins in high doses in combination with radiation and chemotherapeutic agents and their effect on the subsequent survival of growth of human melanoma and squamous cell carcinoma in culture.

Diagnostic Radiology

6. The Senate in its report 103-143, page 125-126, stated, "The Committee expects the Director, in cooperation with the NCI and the Office of Research on Women's Health, to expand support for the

6. The Laboratory of Diagnostic Radiology Research is developing new techniques for evaluating women who either have early stage breast cancer or are at a high risk of developing breast cancer using both

laboratory for diagnostic radiology to further develop those MRI techniques which hold promise for detecting breast and ovarian cancer".	Magnetic Resonance Imaging (MRI) and Position Emission Tomography. Research is underway involving the use of MRI to study tumor perfusion in women with early stage breast cancer. In addition, the LDRR is presently building a prototypic Positron Emission Mammography unit which will be used to aid in the localization of small tumors of the breast, and to study changes in tumor metabolism in response to therapy. In addition, LDRR research on tumor markers using monoclonal antibodies tagged with a biocompatible super-paramagnetic magnetoferritins may provide the increased sensitivity to detect early stages of ovarian cancer. Preliminary research using animal models of malignancy is being evaluated.

Office of Behavioral and Social Science Research

7. The Senate in its report 103-143, page 126, stated, "The Committee is concerned that NIH has not complied with past congressional directives to increase funding of basic and applied behavioral research and expects the Office to ensure that NIH increases significantly the amount of its overall budget devoted to basic and applied behavioral research. The Committee encourages the NIH Director to move quickly to establish the Office. The Committee is particularly interested in NIH increasing its commitment to research in health and behavior, personality research, social and developmental psychology across the lifespan, thinking and cognitive science, treatment effectiveness, psychopathology, and the biological bases of behavior".	7. The establishment of the Office of Behavioral and Social Sciences (OBSSR) and the search for and appointment of its first Director are among the highest priorities of the NIH Director. Administrative procedures to establish the OBSSR and the nationwide search for its first director are underway. It is anticipated that the Office will be operational within this fiscal year. Since funds were not appropriated for the operation of this Office in FY 1994, they will come from the Office of the Director. In FY 1995, the NIH request is $2.5 million for this effort. This request will allow the Office to provide strong leadership in developing: (1) a standard definition for behavioral and social sciences research; (2) a meaningful assessment of current levels of NIH support; and (3) an overall strategy for the expansion and integration of these disciplines across the NIH institutes and centers. The Public Health Service reorganization placing three institutes with substantial behavioral science missions--the National Institute of Mental Health, the National Institute on Drug Abuse, and the National Institute on Alcoholism--strengthens the research portfolio at the NIH. Moreover, the establishment of a central office will provide the infrastructure

needed to achieve full integration of the behavioral and social sciences into the broad spectrum of medical science studies at the NIH.

Endometriosis

8. The Senate in its report 103-143, page 126-127, stated, "The Committee directs the NIH to sponsor a conference that will explore the causes, health consequences, and treatments of little-understood conditions that affect women, including endometriosis. The Committee expects that the conference will be a collaborative effort with significant input from the National Institute on Aging, the National Institute of Environmental Health Sciences, the National Institute of Child Health and Human Development, and the Office of Research on Women's Health".

8. ORWH will be joining with NICHD in a workshop bringing together investigators supported under an RFA co-issued by the two organizations to study the pathophysiology of endometriosis and fibroids. The aim of the workshop will be to develop a research agenda for the treatment of endometriosis and fibriods that builds on the basic research conducted under the RFA. We will use the information presented at this workshop as a starting point to develop an agenda for a broader conference that will include input from a wide range of relevant Institutes.

Aging Research Study

9. The Senate in its report 103-143, page 127, stated, "To realize the full potential of aging research and correct biases against research and career development at NIH, the Committee requests that not later than 6 months after the date of enactment of this act, the Secretary of Health and Human Services shall establish an NIH extramural study section for biomedical aging research for the purpose of reviewing applications for research project grants and other funding mechanisms. This study section shall be comprised primarily of scientists with significant experience and expertise in biomedical aging research. The Committee also expects that scientists with experience and expertise in social and behavioral research will be included in the study section".

9. The Division of Research Grants, NIH, met with the National Institute on Aging to discuss how to best evaluate the scientific and technical merit of those research grant applications of prime relevance to aging research. As a result of these discussions, a Geriatrics and Rehabilitation Medicine Special Emphasis Panel was established and will have its initial meeting in March 1994, This panel will involve approximately 18 members highly competent to review applications in such areas as skeletal problems of aging, muscle physiology and motor control, endocrinology of aging, applied nutrition as it relates to gerontologic syndromes, and rehabilitative and geriatric therapeutic interventions.

Health and Behavior Research

10. The Senate in its report 103-143, page 128, stated, "The newly authorized NIH Office of Behavioral and Social Sciences Research should produce guidelines for the ICD's at NIH to assist them in adhering to the definition. The Committee encourages NIH to expand research on adolescents, including basic research on peer influence and

10. Once the newly authorized Office of Behavioral and Social Sciences Research (OBSSR) is operational, the new Director, with extensive consultation from outside experts, will be charged with the initial responsibility of defining parameters and producing guidelines for conduct and support of "behavioral and social sciences"

decision-making practices, and applied research on prevention of risk that could result in unintentional injury, violence, unintended pregnancy, and sexually transmitted diseases".

research at the NIH. The OBSSR will provide leadership and direction for the development, refinement, and implementation of a trans-NIH plan to identify and coordinate those behavioral and social sciences research projects that should be conducted or supported by the NIH institutes. The overall strategy will be to foster a solid program of basic and applied research that relates individual, group, social, and environmental determinants of human behavior to the promotion of good health and the prevention of risks to various diseases.

NIH Intramural Program

11. The Senate in its report 103-143, page 128, stated, "The Committee urges the NIH Intramural Program to maximize recruitment, mentorship, equitable compensation, promotion, and retention of women, minorities, and scientists with disabilities. While the Committee understands that there are pipeline shortages, it is also convinced that, given sufficient effort, NIH can successfully recruit and retain a diverse and talented pool of women, minorities, and scientists with disabilities who will make significant contributions to the NIH of the future. As one alternative, the Committee recommends an active recruitment program through the identification of individuals currently being supported through the undergraduate and predoctoral programs targeted for women already specifically funded by NIH and NSF".

11. The NIH Intramural Program (IRP) is committed to maximizing its recruitment, mentorship, equitable compensation, promotion, and retention of underrepresented groups of scientists. The IRP has taken a number of significant steps in evaluating the status of underrepresented groups and initiating measures to ameliorate some disparities and problems that could impinge on optimal recruitment, retention, and contributions of these groups. The NIH Office of Education is now exploring the development of a database on underrespresented scientists at the pre- and post-doctoral level who have received NIH funding. This information would form a basis for targeting enhanced recruiting efforts.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Funded Authorizations:						
Office of the Director...............	Title IV, Section 402(b)	40 USC282	Indefinite	$207,861,000	Indefinite	$233,522,000
Total Budget Authority...				$207,861,000		$233,522,000
Funds reimbursed or directly supporting ICDs...................				($154,432,000)		($177,506,000)

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/	
1986	$37,085,000	$117,085,000	$37,574,000	$133,189,000	2/
1986 Sequester				-5,031,000	
1987	36,701,000	246,651,000	56,708,000	57,463,000	3/4/
1988	59,819,000	71,389,000 5/	61,284,000	61,819,000	
1989	59,578,000	71,578,000	65,578,000	72,201,000	
1990	96,570,000	106,987,000	127,570,000	108,468,000	6/
1990 Sequester				-1,049,000	
1991	82,975,000	106,175,000	77,975,000	97,651,000	7/
1991 Sequester				-1,000	
1992	95,176,000	149,176,000	125,724,000	142,112,000	8/
1993	203,430,000	194,275,000	188,400,000	190,325,000	9/
1994	234,907,000	224,746,000	241,225,000	233,605,000	
1995	233,522,000 10/				

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Includes $20,000,000 for the continuation of a program that supports biomedical research in small and minority schools and universities, and $70,000,000 for research on AIDS. Includes $16,197,000 transfer from HRSA for establishment of the National Center for Nursing Research.

3/ Includes a transfer of $755,000 to cover the FERS increase and partial costs of the pay raise.

4/ The Budget Estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes.

5/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

6/ Excludes enacted administrative reduction of $519,000.

7/ Excludes enacted administrative reductions of $2,924,000.

8/ Excludes enacted administrative reductions of $1,459,000, and enacted rescission of $258,000.

9/ Excludes enacted administrative reductions of $2,438,000.

10/ The 1995 request excludes funds for HIV Research Activities proposed for consolidation in the NIH Office of AIDS Research.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Authority by Activity
(Dollars in thousands)

	1991 1/ Actual		1992 1/ Actual		1993 1/ Actual		1994 1/ Appropriation		1995 1/ Estimate		Changes	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research Management and Support	638	$82,610	665	$129,853	716	$175,311	717	$207,861	704	$233,522	-13	+$25,661
Unobligated balance start of year	---	---	---	-1,504	---	---	---	---	---	---	---	---
Unobligated balance end of year	---	1,506	---	1,867	---	---	---	---	---	---	---	---
Subtotal obligations	---	84,116	---	130,216	---	175,311	---	207,861	---	233,522	---	+25,661
Unobligated balance lapsing	---	291	---	249	---	70	---	---	---	---	---	---
Total budget authority	666	84,407	699	130,465	716	175,381	717	207,861	704	233,522	-13	+25,661
Funds reimbursed or directly supporting ICDs		(47,438)		(85,952)		(127,808)		(154,432)		(177,506)		(+23,074)

1/ The FY 1991 actual, FY 1992 actual, FY 1993 actual, the FY 1994 appropriation, and the FY 1995 estimate excludes $513,000, $1,128,000, $9,277,000, $9,277,000 and $9,277,000 respectively, in permanent budget authority expected to be realized from Cooperative Research and Development Agreements.

Note: Includes FTEs associated with HIV Research Activities. Funds to support these FTEs are included in the NIH Office of AIDS Research.

Justification

Office of the Director

FY 1993 Authority		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
716	$175,381,000	717	$207,861,000	704	$233,522,000	-13	+$25,661,000
	(127,808,000)*		(154,432,000)*		(177,506,000)*		(+23,074,000)*

*Funds Reimbursed or Directly Supporting ICDs.

General Statement

This document provides justification for the FY 1995 Non-AIDS activities of the Office of the Director (OD). Justification of NIH-wide FY 1995 AIDS can be found in the NIH section entitled "Office of AIDS Research (OAR)". The appropriation for the (OD) of the National Institutes of Health (NIH) provides funds for the central administration of, and services to, the NIH Institutes, Centers and Divisions (ICDs). While each major research component of the NIH administers the activities associated with its specific programs, the Office of the Director is responsible for their overall direction and coordination. The major units within the OD are responsible for central functions such as extramural and intramural research policy and the coordination of scientific policy; coordination and direction of research on the health of women and minorities as well as research training programs for these populations; legislation, program planning and evaluation; coordination of public affairs and communication activities; contract and grant administration; and financial and personnel management. A number of other offices are responsible for promotion of disease prevention, medical applications of research, and for NIH-wide direction and centralized services in such areas as equal opportunity, procurement, and information resources management.

During the last five years there has been substantial growth in the OD appropriation. However, a great portion of this growth has been in programs of a cross-cutting nature such as the Women's Health Initiative, the Minority Health Initiative, and the Science Education and the Alternative Medicine Programs. While funds are initially budgeted in the OD, and the OD provides the overall direction, coordination and oversight, actual program operations are conducted within the ICDs. The majority of these funds are reimbursed to ICDs for their direct support of the specific programs.

The President's appropriation request of $233,522,000 for this account represents current law requirements. No proposed law amounts are included.

Funding for the Office of the Director during the last five years has been as follows:

	Amount	Funds Reimbursed or Directly Supporting ICDs	FTE
FY 1990	79,632,000	(44,463,000)	626
FY 1991	84,407,000	(47,438,000)	666
FY 1992	130.465,000	(85,952,000)	699
FY 1993	175,381,000	(127,808,000)	716
FY 1994	207,861,000	(154,432,000)	717

Purpose and Method of Operation

The Office of the Director provides leadership and direction to the NIH research community, and coordinates and directs initiatives which cross-cut the NIH. The OD is responsible for the development and management of intramural and extramural research and research training policy, the review of program quality and effectiveness, the coordination of selected NIH-wide program activities, and the administration of centralized support activities essential to operations of the NIH.

Several offices in the OD provide policy and direction to the NIH research community:

The Office of Extramural Research (OER) advises the NIH Director on matters relating to extramural research; develops and implements regulations, policies, and procedures governing the stewardship of extramural research and training programs and the peer review of extramural award mechanisms (grants, contracts, cooperative agreements, and fellowships). The Office ensures that certain conditions of DHHS and PHS awards, including the protection of human subjects, the welfare of animals, and the inclusion of minorities and women in study populations, comply with Federal requirements.

The Office of Intramural Research (OIR) provides leadership, direction and management to the intramural research community with the goal of maintaining a stimulating environment for scientific talent to conduct highly creative bench-to-bedside biomedical and fundamental research of the highest quality. The OIR develops guidance for the protection of human subjects and laboratory animals; provides a premier research program and facility for diagnostic radiology research; provides purified HIV proteins for structural, physicochemical and pharmacological studies; and administers the education program for talented students and postdoctoral scientists.

The Office of Disease Prevention (ODP) provides leadership, direction, and support to science and biomedical programs that seek to improve the nation's health through research, research training, and the international exchange of knowledge. The ODP has the responsibility for the coordination of the Disease

Prevention and Health Promotion research programs of the component ICDs of the NIH. The ODP also has the responsibility for conducting the Women's Health Initiative and for development of Consensus Development Conferences.

The Office of Research on Women's Health (ORWH) serves as the focal point for women's health research at NIH in promoting and directing research, securing and monitoring the inclusion of women in clinical studies, and enhancing career development of women into biomedical careers. The ORWH achieves these efforts through collaboration with the NIH ICDs and, by extension, the scientific community and public, to assure that women's health research becomes an integral part of biomedical and behavioral research and that women are recruited into and enhanced in their scientific careers.

The Office of Research on Minority Health (ORMH) is responsible for the coordination of minority health and training activities at the NIH. The mission of the office is two-fold (1) to improve the health status of minorities and (2) to increase the participation of minorities in biomedical research. The ORMH's strategy for accomplishing this mission is to work with the NIH's ICDs, other government agencies, majority and minority institutions, and community organizations to develop and fund minority health and training programs. The centerpiece of ORMH activities is the Minority Health Initiatives (MHI). This multi-component project supports research activities that address health issues across the lifespan -- infant mortality, child health, health behaviors of adolescents and young adults, and the health of aging minorities. The MHI also supports research training activities that promote the participation of minorities in all stages of the educational pipeline -- precollege, junior college, undergraduate, graduate, and postdoctoral studies.

The Office of Science Policy and Technology Transfer (OSPTT) provides leadership, direction and coordination on all phases of science policy and technology transfer. OSPTT addresses issues in areas where science interfaces with society-at-large. These include a broad array of ethical, legal, social and economic issues that emerge from biomedical and behavioral research. OSPTT also manages technology transfer activities, providing advice, assistance as well as direct services to all PHS agencies. Strategic planning and program evaluation as well as legislative policy and analysis constitute other major components of OSPTT. Other programs within OSPTT address science education, alternative medicine and rare diseases. OSPTT also provides program direction and support to the Advisory Committee to the Director, NIH, and the Recombinant DNA Advisory Committee.

There are also a number of administrative and managerial support functions in the Office of the Director:

The Office of Communications (OC) seeks to achieve greater understanding of NIH programs, activities, and research accomplishments on the part of the general public, Congress, biomedical institutions and the medical profession. The OC also coordinates the public affairs and other communication activities of the ICDs.

The Office of Equal Opportunity (OEO) advises the Director, NIH, and staff on matters related to the Equal Employment Opportunity (EEO) programs and policies of NIH. The OEO maintains liaison with NIH components that administer programs to increase the participation of minorities in biomedical research; provides for investigation of discrimination complaints; and assures complaint counseling and fair and judicious processing of such complaints.

The Office of Management, is responsible for providing leadership and guidance in all phases of management and advises the NIH Director and his staff in the areas of information resources management, budget and financial management, personnel management, management assessment and internal control, grant and contract management, procurement, logistics, engineering services, safety, space and facility management, and security operations.

Overall Budget Policy

The FY 1995 budget request for the Office of the Director is $233,522,000. This represents an increase of $25,661,000 over the comparable FY 1994 level of $207,861,000. Essentially all of the increase is for trans-NIH programs where the funding will be reimbursed to the ICDs for the programs or research contracts in support of these programs.

This request includes $61,252,000 for the Women's Health Initiative, and $15,926,000 for the Office of Research on Women's Health. Also, the request includes $66,478,000 for the Minority Health Initiative and $10,421,000 for the Office of Research on Minority Health. Other highlights include $10,000,000 for the Director's Discretionary Fund, $13,643,000 for the Academic Research Enhancement Award (AREA) Program, $2,053,000 for the Diagnostic Radiology Research Program, $3,694,000 for Office of Alternative Medicine, $1,929,000 for Science Education, $1,000,000 for the Loan Repayment Program, $2,500,000 for the Office of Behavioral & Social Sciences Research and $44,626,000 for the central OD program offices.

The request includes 704 FTEs, a decrease of 13 below the FY 1994 level of 717.

Women's Health Initiative

The Women's Health Initiative is a large integrated study of prevention of the leading causes of death, disability, and frailty in postmenopausal women. Components of the study include: a clinical trial to test promising preventive interventions for cancer, heart disease, and osteoporosis; an observational study to define new predictors and biomarkers for disease and risk status; and a community prevention study to test approaches to improving healthful behaviors of minority women. The goal of these studies is valid information for women and their health providers about prevention of disease and disability.

The 16 Vanguard Clinical Centers for the clinical trial were awarded in FY 1993 and enrollment of participants for the clinical trial and observational study began in September 1993. The interest in joining the study has been extraordinarily high. An additional 29 clinics will be added in FY 1994 and the full-scale recruitment will begin in the fall of FY 1994. Recruitment of the 163,000 participants will require 3 years, and 9 years of follow-up thereafter are planned. There will be 63,000 women in the clinical trial component and 100,000 women in the observational study. To facilitate a recruitment target of 20% minorities, one-quarter of the clinical centers will be clinics that focus on minority recruitment and retention using culturally appropriate approaches. A committee appointed by the Institute of Medicine (IOM) reviewed the program and indicated that it should proceed but has made some suggestions for improvement. The NIH Director is reviewing the recommendations of the IOM and will make a decision by spring.

The Community Prevention Study will focus on communities with substantial minority or medically underserved populations that have experienced little beneficial change in risk factors for disease. Community organizations and appropriate information channels will act as change agents and the effectiveness of the programs will be evaluated. The goal is to develop validated models and approaches for widespread public health application. The program will be supported by grants under a cooperative agreement. The request for applications has been released and awards are anticipated by September 1994. Close monitoring of the activities of this large study will assure that the concerns of the Congress are evaluated.

Minority Health Initiative

The Minority Health Initiative (MHI), begun in FY 1992, is the centerpiece of the Office of Research on Minority Health's (ORMH) program activities. The goals of the initiative include increasing intramural and extramural research aimed at improving minority health across the lifespan, developing proven protocols for intervention in health behaviors affecting the longevity and quality of life for minorities, and implementing programs that prepare more minorities for careers in the biomedical sciences. In FY 1993, the ORMH successfully completed the launching of the MHI.

The Infant Mortality component of the MHI supports community based epidemiological and clinical research to address the problem of the unacceptably high infant mortality rate in Washington, D.C. In FY 1993, protocols for three major studies were developed. These studies will be initiated early in FY 1994. This program is funded at $5,000,000 for FY 1994.

An additional component of the MHI focuses on children's health, including injury-related morbidity, lead poisoning, asthma, and hearing and speech impairment. As part of this component, in FY 1994, the ORMH and the National Institute of Environmental Health Sciences will launch a major research initiative to address the etiology and treatment of a variety of environmentally related health problems in minority children. ORMH is providing $7,000,000 for this component in FY 1994.

The Youth Behavior initiative focuses on evaluating and comparing various community based interventions for decreasing violence related injuries and deaths, sexually transmitted diseases, and unintended pregnancies in minority youth ages 10-24. In FY 1993, seven research sites received second year funding. FY 1994 activities will include collecting and analyzing data and implementing the community programs. This component is funded at $5,000,000 for FY 1994.

The MHI includes $6,000,000 in the FY 1994 budget for a variety of research projects, both intramural and extramural, related to the health problems of young adults. In FY 1993, ORMH supported research projects with several of the ICDs involved in investigating glaucoma, AIDS, lupus, diabetes, hemochromatosis and tuberculosis. In FY 1994, research will be conducted on enviromentally related health problems, obesity and hypertension. Additionally, ORMH funds will support efforts to recruit and retain more minorities in clinical trials.

The aging component of the MHI funds research centers for the study of diseases and conditions that lead to ill health and disability in older minority populations. Six center grants were awarded in FY 1993 for research on such conditions as hypertension, cancer, diabetes and arthritis. This component is funded at $2,000,000 for FY 1994.

A number of training components are also included in the MHI. The Bridges to the Future program, which is administered by the National Institute of General Medical Sciences, provides linkages for minority students between two-year and four-year colleges and between terminal M.S. degree programs and Ph.D. programs -- two key transition points for students considering research careers. In FY 1993, thirty-nine awards were made. In FY 1994, this program will be supported at $10,000,000.

In collaboration with the Fogarty International Center, the ORMH is implementing an international research training program to encourage undergraduate, graduate and post-graduate minority students to pursue foreign research experiences. In FY 1993 fifteen grants were awarded to a total of twenty institutions. This program will receive $4,000,000 in funds for FY 1994.

The NIH is collaborating with the National Science Foundation (NSF) on an effort to expand and emphasize biomedical components in previously established NSF programs. In 1994 this effort is funded at $2,500,000.

The ORMH also supplements pre-existing minority training programs sponsored by the ICDs. In FY 1993 these programs included Minority Biomedical Research Support, Minority Access to Research Careers, and Research Centers in Minority Institutions among others. From the FY 1994 budget, $3,478,000 will support these programs as well as various training and teacher enrichment programs administered by the ICDs. In FY 1994, $2,500,000 will support the NIH Minority Supplement Program which provides funds, through the ICDs, to researchers receiving NIH grants to train minority students and investigators.

From the FY 1994 budget, $9,000,000 will be devoted to identifying and filling gaps in the NIH's minority research and training portfolio by developing new components of the MHI. The program agenda of the MHI is based on the recommendations developed by the ORMH Fact Finding Team in 1992. As implemented in FY 1993, the MHI addresses most, but not all, of the thirteen recommendations of the Fact Finding Team. Recommendations that remain to be fully translated into MHI components include those addressing research on chronic diseases, the expansion of NIH programs at minority institutions, and the recruitment of minority students into the sciences.

Research on Women's Health

The Office of Research on Women's Health (ORWH) continues its strong collaboration with the NIH ICDs to direct programs, initiatives, and activities in women's health research and women's biomedical research careers. The research agenda, defined in FY 1991, remains a dynamic process with finement as necessary based on evolving science and clinical implementation. In FY 1993, ORWH focused attention on fourteen specific areas of women's health that have had insufficient research attention. Such areas included studies on lung cancer in women, coronary artery and thrombotic disease, prevalence of risk factors for disease among women of different racial and ethnic groups, violence against women and post-traumatic stress disorder, and depression and its interaction with other health problems. The inclusion of the Alcohol, Drug Abuse, Mental Health Association (ADAMHA) research institutes has made an important contribution to the totality of women's health and the mind/body interaction. ORWH made 78 awards to on-going research in these fourteen areas. Of the awards made, 88 percent were directed toward clinical research with the remaining 12 percent in basic research. Forty-one percent of the Principal Investigators are female which is an increase from the 36 percent in FY 1992.

In addition to the administrative supplements, ORWH directed collaborative funding with the NIH ICDs on special initiatives, e.g., those unanticipated projects that do not necessarily fit within the directed research portfolio, but provide exciting opportunities for research action. In FY 1993, ORWH funded thirteen special initiatives which ranged from the computerization of the Carnegie Collection of Human Embryos to the multiple roles of middle generation caregiving women. Research conferences and workshops, which assist in setting future research agenda were also a key part of ORWH planning. Fifteen conferences were supported including five regional meetings on Hispanic health, women's urological health research symposium, and a workshop on topical microbicides. Future planning has moved forward with the decision to direct program research in four major areas: women's urological health, reproductive health and sexually transmitted diseases, autoimmune diseases in women, and occupationally-related diseases and disabilities. The focus in these four areas will not preclude research action by ORWH in other areas of women's health.

The ORWH continues to monitor the compliance of women in clinical studies at NIH. This year, in response to the NIH Revitalization Act of 1993 (Public Law 103-43), ORWH, in collaboration with the OD and the ORMH, created the revised policy on Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. This new policy substantially extends the 1990 policy and requires the inclusion of minority subpopulations and valid analyses of gender and racial/ethnic differences in Phase III clinical trials. In addition, the law requires that the NIH support outreach activities and programs concerning recruitment of women and minorities into such studies. In response to this legislation, ORWH, and OD, are preparing and will disseminate "The NIH Notebook on Inclusion of Women and Minorities in Clinical Research." This notebook will serve as a primer for scientists wishing guidance on how to appropriately recruit and retain women, particularly minority women, in clinical studies.

Prior to the issuance of the Act, the ORWH had already been actively involved in such efforts. This year the ORWH sponsored a public hearing and scientific workshop on the "Recruitment and Retention of Women in Clinical Studies." Proceedings from the workshop will be published in FY 1994. The ORWH contract with the Institute of Medicine has resulted in a report. "Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies." This report will be released in March 1994.

The third part of the ORWH mandate, recruitment and advancement of women in biomedical research has proceeded expeditiously. The report from the workshop, "Women in Biomedical Careers" is about to be released. This year the ORWH collaborated, with the National Institute of Nursing Research, on a Research Career Program Award. The ORWH continued support of the National Cancer Institute Scientific Enrichment Program, an effort directed toward recruitment of youth, especially minority youth, into science careers. The pilot programs for reentry of scientists to careers interrupted for family responsibilities continued. The first award to an intramural scientist was made through the Office of Education with the Office of Intramural Affairs. Other candidates are currently being considered. Within the extramural community, six awards were made to women scientists and their mentors, Principal Investigators on NIH-supported studies. The ORWH considers this latter program now ready for adoption by NIH institutes and centers and recently made such a recommendation. The National Institutes of Neurological Disorders and Stroke has already initiated such a program.

Research on Minority Health

The Office of Research on Minority Health (ORMH) is the coordinating office for minority health research and research training efforts at the NIH. The ORMH's mission is two-fold: (1) to improve the health status of all minorities across the lifespan and (2) to increase the numbers of minorities pursuing careers in the biomedical sciences. To accomplish this mission the ORMH develops and supports projects with the various ICDs that comprise the NIH, other government agencies and outside organizations.

In FY 1993, the ORMH's $9,048,000 operating budget was used for staffing and to complete the launching of the MHI. In FY 1994, the $9,887,000 budget will be utilized to support the addition of five new employees, bringing the ORMH to its authorized staffing level of eight. Additionally, this budget will fund technical assistance workshops, conferences, program evaluation, initiatives to recruit and retain minorities in clinical trials, and outreach to Historically Black Colleges and Universities, other educational institutions and scientific organizations.

The budget will also support a project initiated by ORMH to evaluate minority training programs at the NIH. In FY 1993, the ORMH released Phase I of the assessment which summarizes data on program participation rates. In FY 1994, Phase II of the assessment will be implemented and will include delineation of the goals and objectives of the programs and a needs assessment for a tracking system to monitor program effectiveness.

Science Education

The Office of Science Education Policy (OSEP) provides leadership, direction, and coordination for all phases of policy regarding NIH and DHHS life sciences education efforts. It serves as a central source of information on the broad array of NIH, Federal and private sector science education programs. The OSEP also oversees the development, initial operation, evaluation, and dissemination of innovative science education programs including: the Science Education Partnership awards (SEPA), a grant program encouraging the development of creative partnerships between educators and researchers; the Biomedical Research Advancement: Saturday Scholars (BRASS) program, a Saturday morning science education program for middle school students; and a new NIH Mini-Medical School, an evening lecture series designed to teach the general public about the biomedical health sciences. OSEP with NCRR will provide follow-up funding so that the most successful SEPA projects can be disseminated nationwide. The BRASS program, now in its third year on the NIH campus, will pilot test its curriculum at the University of Tennessee and Boston University. The first Mini-Medical School series is scheduled to begin in the spring of 1994.

In addition, OSEP serves as the focal point for DHHS involvement in the Federal Coordinating Council for Science, Engineering and Technology (FCCSET) Committee on Education and Technology (CET) and provides leadership for the PHS Life Sciences Education and Science Literacy Board.

Office of Alternative Medicine

During FY 1993 the Office of Alternative Medicine (OAM) was involved in holding six grant writing workshops throughout the United States. This was done in preparation for training applicants to respond to a grant announcement, written by the OAM, and entitled "Exploratory grants in Alternative Medicine". Eight hundred letters of intent were subsequently received and over 450 grants reviewed of which 252 were scored. Thirty grants were awarded at a cost of $900,000. An additional 12 grants, pending FDA approval for studies on specific therapies, will be awarded in FY 1994. A cancer therapy involving antineoplastins continues to be evaluated in conjunction with NCI. A comprehensive review of the field of Alternative Medicine, is being prepared.

During FY 1994 the goals of the OAM include: the solicitation of studies from clinicians and researchers presenting retrospectively data on treatment outcomes for the purpose of validation for efficacy as well as prospective studies; finalizing the charter; establishing the National Advisory Council, which was mandated by Congress, for the purpose of providing advice to the Director of OAM; convening, through the Office of Medical Applications of Research, two national conferences on methodology of relaxation therapy; as well as providing ongoing grant-writing training for applicants.

Academic Research Enhancement Award Program

The Academic Research Enhancement Award (AREA) program is designed to provide support of new or expanded health-related research projects conducted by faculty in undergraduate institutions that are not research-intensive. A significant number of America's research scientists receive training at these educational institutions. The AREA funds create a research opportunity for these institutions, faculty, and students to participate in the nation's biomedical and behavioral research effort. In FY 1993, 127 AREA awards amounting to $12,900,000 were issued, as compared to 152 awards totaling $15,200,000 (including $1,000,000 from the Director's Discretionary Fund) for the previous year.

Director's Discretionary Fund

The Director's Discretionary Fund (DDF) enables the Director, NIH, to be more responsive to emerging research opportunities and health priorities.

During FY 1993 the DDF provided $3,255,000 to support 93 Shannon Awards and $7,000,000 to support the National Center for Human Genome Research Intramural Program.

Office of the Director

Research Management and Support

FY 1993 Actual		FY 1994 Appropriation		FY 1995 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
716	$175,381,000	717	$207,861,000	704	$233,522,000	-13	+$25,661,000
	(127,808,000)*		(154,432,000)*		(177,506,000)*		(+23,074,000)*

*Funds Reimbursed or Directly Supporting ICDs.

The Office of the Director (OD) supports research and research training in the biomedical sciences through the formulation and coordination of NIH policy. The President's appropriation request of $233,522,000 for this account represents current law requirements. No proposed law amounts are included. Funding for the Office of the Director during the last five years has been as follows:

	Amount	Funds Reimbursed or Directly Supporting ICDs	FTEs
FY 1990	79,632,000	(44,463,000)	626
FY 1991	84,407,000	(47,438,000)	666
FY 1992	130,465,000	(85,952,000)	699
FY 1993	175,381,000	(127,808,000)	716
FY 1994	207,861,000	(154,432,000)	717

Rationale for the Budget Request

The FY 1995 budget request for the OD is $233,522,000 an increase of $25,661,000 over the FY 1994 estimate of $207,861,000. Following are current activities and future plans for the following programs:

Policy and Direction Offices

The FY 1995 request for the Office of Research on Women's Health (ORWH) will enable this office, with a budget of $15,926,000 and a staff consisting of Director and 13 employees, to continue to refine its programs and activities in women's health research, inclusion of women in clinical research, and women's biomedical career development. This is an increase of $5,601,000 over the FY 1994 level. The partnerships that the ORWH has established both within and outside the NIH will continue and will be enhanced as new opportunities evolve.

The ORWH will continue its general research activities in women's health across the life span and racial/ethnic groups, while focusing a directed research program in four areas: women's urological health, reproductive health and sexually transmitted diseases, autoimmune diseases in women, and occupationally-related diseases and disabilities. The ORWH will direct attention to a number of efforts required by the new legislation on the inclusion of women and minorities in clinical research. Such activities range from the expeditious implementation of the guidelines and education of the scientific community to a clearinghouse on women's health with a registry of clinical trials. Recommendations from the ORWH public hearing and workshop on the recruitment and enhancement of women in biomedical careers will be combined with the directions for action on women in biomedical careers contained in the NIH Revitalization Act of 1993.

The FY 1995 request for the Office of Research on Minority Health (ORMH) is $10,421,000, an increase of $534,000 over the FY 1994 level. This budget funds all of the support activities and operational costs of the Minority Health Initiative. In part, the increase will provide for additional support activities -- staff, oversight, evaluation, outreach, etc. -- as new initiatives are implemented under the Minority Health Initiative. As the trans-NIH minority office, the ORMH will also provide increased coordinating and monitoring activities necessary as the institutes increase their minority health research and research training programs.

Minority Health Initiative

The FY 1995 request for the Minority Health Initiative (MHI) is $66,478,000, an increase of $10,000,000 over the FY 1994 level. As approximately 60% of the FY 1994 budget for the MHI is comprised of multi-year programs, the majority of increase in funds for FY 1995 will allow for expansion of these programs, including the funding of additional grantees and supplemental studies relevant to the primary initiative. The request provides $5,000,000 to continue research on the determinants of infant mortality and the development of successful intervention strategies. The request also includes $7,000,000, an increase of $3,000,000 over the FY 1994 level, for research on the health of minority children, including such health conditions as asthma, vision and speech impairment and environmentally related diseases. The MHI budget provides $5,000,000 to continue support of a community-based research initiative that will develop interventions to reduce violence, substance abuse, sexually transmitted diseases and early pregnancy in minority adolescents. The budget will also provide $6,502,000, an increase of $502,000 over the FY 1994 level, to fund the young adult component of the MHI. This component supports research on AIDS, glaucoma, tuberculosis, hypertension and other diseases impacting the quality and longevity of life of minority adults. The request also provides $2,000,000 for the support of research on the health of minority aging populations.

The increase will also be used to expand the minority biomedical research training programs in the MHI. The request provides $2,500,000 for pre-college programs, conducted in collaboration with NSF, that are designed to attract more minority students into the sciences. Six million dollars will be used to support the 2-year/4-year Bridges to the Future program which assists minority students in junior colleges in making the transition to baccalaureate programs. The MHI also provides $6,000,000, an increase of $1,000,000 over the FY 1994 level, for the M.S./Ph.D. program to encourage students in terminal M.S. programs to enter doctoral programs. Of the request, $4,500,000, an increase of $500,000 over the FY 1994 level, will be used to fund the Minority International Research Training Program. This program offers minority students the opportunity to pursue foreign research training. The increase will also support the NIH Supplemental program in the amount of $2,500,000. This program provides funds, through the ICDs, to researchers receiving NIH grants to train minority students and investigators.

From the FY 1995 request, $19,476,000, an increase of $4,998,000 over the FY 1994 level, will be devoted to identifying and filling gaps in the NIH's minority research and training portfolio by developing new components of the MHI. The current program components of the MHI were developed in response to a series of recommendations made by the ORMH Fact Finding Team in 1992. In its current form, the MHI addresses the majority of the thirteen recommendations of the Fact Finding Team.

Office of Behavioral and Social Sciences Research

The FY 1995 request for the Office of Behavioral and Social Sciences Research (OBSSR) is $2,500,000. This request will allow the Office to provide leadership and direction in the development, refinement, and implementation of an NIH research strategy for the conduct and support of behavioral and social science research and to educate the biomedical community and the general public about individual, familial, social, and environmental factors that contribute to the promotion of good health and the prevention, treatment, and cure of disease. The mission of the OBSSR is to develop a standard definition of behavioral and social sciences and provide a prominent focus within the NIH for coordinating research conducted and supported by the NIH/ICDs.

The OBSSR will develop an overall plan to evaluate the importance of multifactorial lifestyle determinants that interface with medicine and contribute to the promotion of good health and the prevention of disease. The office will foster basic and clinical research in the behavioral and social sciences to identify behavioral factors that contribute to the Nation's public health problems and to apply this information to help reduce the morbidity and mortality from the leading causes of death.

The OBSSR will foster a comprehensive research program; increase support for behavioral and social sciences research at the NIH; supplement current NIH/ICD research and research training programs; stimulate cross-cutting research initiatives; promote multidisciplinary research; and integrate a biobehavioral perspective into research on the promotion of good health and the prevention, treatment, and cure of disease.

Loan Repayment Program

In FY 1995 the request includes $1,000,000 to fund Scholarship and Loan Repayment Programs authorized under the NIH Revitalization Act of 1993 (P.L. 103-43). The Scholarship Program, directed at individuals from disadvantaged backgrounds, provides scholarships for pursuing, as undergraduates at accredited institutions of higher education, academic programs appropriate for careers in professions needed by the NIH. Individuals receiving scholarships agree to serve as employees of the NIH in positions that are needed and for which the individuals are qualified. The Loan Repayment Program provides for contracts with appropriately qualified health professionals from disadvantaged backgrounds, to conduct clinical research as employees of the NIH. The NIH agrees to pay, for each year of such service, not more than $20,000 of the principal and interest of the educational loans of the health professionals.

The FY 1995 request also provides $10,000,000 for the Director's Discretionary Fund, $13,643,000 for the Academic Research Enhancement Award Program, $61,252,000 for the Women's Health Initiative, $2,053,000 for the Laboratory for Diagnostic Radiology Research, $1,929,000 for Science Education, $3,694,000 for the Office of Alternative Medicine and $44,626,000 for OD operations which includes $500,000 to strengthen Office of Equal Opportunity functions.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Detail of Full-Time Equivalent Employment (FTE)

	1993 Actual	1994 Estimate	1995 Estimate
Office of Director 1/.....	716	717	704

Average GS/GM Grade

1990..................................	10
1991..................................	10
1992..................................	10
1993..................................	10
1994..................................	10
1995..................................	10

1/ Includes 37 FTEs in FY 1993, 39 FTE's in FY 1994 and 38 FTEs in FY 1995 associated with AIDS Research Activities.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

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NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research
(INCLUDING TRANSFER OF FUNDS)

For carrying out Part D, of Title XXIII of the Public Health Service Act, $1,379,052,000, of which $10,000,000, to remain available until expended, is for the Emergency Discretionary Fund authorized by section 2356 of the Act: Provided, That the Director of the Office of AIDS Research shall transfer funds from this appropriation to each appropriation account of the National Institutes of Health that will fund AIDS activities under the Comprehensive Plan developed under Section 2353 of the Act, the amount necessary to carry out subsection (d) of that section.

Office of AIDS Research

Language Analysis

Language Provision	Explanation
"For carrying out Part D, of Title XXIII of the Public Health Service Act, $1,379,052,000, of which $10,000,000, to remain available until expended, is for the Emergency Discretionary Fund authorized by section 2356 of the Act: Provided, That the Director of the Office of AIDS Research shall transfer funds from this appropriation to each appropriation account of the National Institutes of Health that will fund AIDS activities under the Comprehensive Plan developed under Section 2353 of the Act, the amount necessary to carry out subsection (d) of that section.	*This language provides all funds to the Director, Office of AIDS Research (OAR) for the research activities with respect to Acquired Immune Deficiency Syndrome (AIDS) for the National Institutes of Health. It further provides for an emergency discretionary fund that will remain available until expended. The Director, OAR shall transfer funds from this account to each Institute, Center, or Division that will conduct AIDS activities provided for under the Comprehensive Plan, the amount necessary to carry out its AIDS activities with respect to the Plan.*

Office of AIDS Research

Amounts Available for Obligation

	1993 Actual	1994 Appropriation	1995 Estimate
Appropriation.........	---	---	$1,379,052,000
Subtotal, Adjusted appropriation.....	---	---	1,379,052,000
Comparative transfers from:			
National Cancer Institute...........	$173,029,000	$213,457,000	---
National Heart, Lung, and Blood Institute.	48,058,000	54,977,000	---
National Institute of Dental Research.....	8,375,000	11,431,000	---
National Institute of Diabetes and Digestive and Kidney Diseases.....	6,446,000	10,438,000	---
National Institute of Neurological Disorders and Stroke	18,416,000	22,105,000	---
National Institute of Allergy and Infectious Diseases.	459,698,000	544,791,000	---
National Institute of General Medical Sciences...........	16,850,000	23,945,000	---
National Institute of Child Health and Human Development...	38,807,000	56,426,000	---
National Eye Institute	6,283,000	8,381,000	---
National Institute of Environmental Health Sciences...........	4,272,000	5,608,000	---
National Institute on Aging..............	1,153,000	1,664,000	---

	1993 Actual	1994 Appropriation	1995 Estimate
National Institute of Arthritis and Musculoskeletal and Skin Diseases.......	$1,760,000	$2,795,000	---
National Institute on Deafness and Other Communication Disorders...........	618,000	1,507,000	---
National Institute of Mental Health.......	78,433,000	87,182,000	---
National Institute on Drug Abuse..........	127,047,00	143,376,000	---
National Institute of Alcohol Abuse and Alcoholism..........	6,823,000	9,457,000	---
National Institute of Nursing Research....	2,966,000	4,444,000	---
National Center for Research Resources..	50,881,000	61,383,000	---
John E. Fogarty International Center for Advanced Study in the Health Sciences.	5,684,000	8,852,000	---
National Library of Medicine............	1,101,000	3,082,000	---
Office of the Director	14,757,000	25,744,000	---
Subtotal, adjusted budget authority...	1,071,457,000	1,301,045,000	1,379,052,000
Unobligated balance, available start of year.............	25,405,000	21,652,000	---
Unobligated balance, available end of year.............	-21,652,000	---	---
Unobligated balance lapsing............	-1,253,000	---	---
Total, obligations..	1,073,957,000	1,322,697,000	1,379,052,000

NATIONAL INSTITUTES OF HEALTH

AIDS Budget Mechanism

	1993 Actual		1994 Appropriation		1995 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research projects:						
Noncompeting	900	$314,816,000	1024	$378,674,000	1180	$478,300,000
Administrative supplements	(62)	8,045,000	(12)	1,001,000	(12)	1,042,000
Competing projects:						
Renewals	170	70,634,000	191	73,678,480	139	53,543,000
New	319	93,087,000	373	109,825,520	257	79,360,000
Supplemental	12	2,186,000	34	6,862,000	17	3,012,000
Subtotal, competing	501	165,907,000	598	190,366,000	413	135,915,000
Subtotal, research projects	1401	488,768,000	1622	570,041,000	1593	615,257,000
Research Centers:						
Specialized/comprehensive	31	49,364,000	34	60,458,000	34	63,927,000
General Clinical Research	--	24,328,000	--	29,625,000	--	31,457,000
Biomedical research technology	--	705,000	--	854,000	--	954,000
Comparative medicine program	11	19,117,000	11	22,243,000	11	23,351,000
Biological models and materials research	--	174,000	--	250,000	--	250,000
Research centers in minority institutions	--	4,651,000	--	5,397,000	--	5,667,000
	42	98,339,000	45	118,827,000	45	125,606,000
Other Research:						
Research career programs	63	5,618,000	80	7,455,000	79	7,601,000
Cancer education	--	---	--	---	--	---
Cooperative clinical research	17	12,618,000	16	13,743,000	16	14,880,000
Biomedical research support	--	291,000	--	659,000	--	659,000
Minority biomedical research support	--	391,000	--	407,000	--	428,000
Other research	96	12,409,000	110	19,325,000	111	17,977,000
Subtotal, other research	176	31,327,000	206	41,589,000	206	41,545,000
Total, research grants	1619	618,434,000	1873	730,457,000	1844	782,408,000

Research Training:						
Individual awards:						
Noncompeting	33	807,000	39	965,000	76	2,181,000
Competing projects	31	691,000	58	1,691,000	21	523,000
Subtotal, individual	64	1,498,000	97	2,656,000	97	2,704,000
Institutional awards:						
Noncompeting	441	10,762,000	444	11,915,000	530	14,075,000
Competing projects	124	2,564,000	191	4,895,000	105	3,003,000
Subtotal, institutional	565	13,326,000	635	16,810,000	635	17,078,000
Total, research training	629	14,824,000	732	19,466,000	732	19,782,000
Research and development contracts	264	206,539,000	337	269,822,000	353	288,554,000
Intramural research		165,479,000		193,931,000		198,397,000
Research management and support		50,323,000		58,543,000		60,059,000
Subtotal, ICDs		1,055,599,000		1,272,219,000		1,349,200,000
National Library of Medicine		1,101,000		3,082,000		3,191,000
Office of the Director		14,757,000		25,744,000		26,661,000
Building and Facilities		---		---		---
TOTAL		1,071,457,000		1,301,045,000		1,379,052,000
Clinical Trials		(288,379,000)		(337,985,000)		(349,234,000)

Note: FTEs associated with HIV/AIDS Research activities are included in the justifications of the Institutes Centers, and Divisions.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Summary of Changes

1994 Estimated budget authority	$1,301,045,000
1995 Estimated budget authority	1,379,052,000
Net change	+78,007,000

	1994 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
Changes:				
A. Built-in:				
1. Intramural research:				
a. Within grade increases		$41,694,000		+$570,000
b. One less day of pay		41,694,000		-164,000
c. Annualization of January 1994 locality pay increases		41,694,000		+315,000
d. January 1995 pay increases		41,694,000		+475,000
e. Increase in unemployment compensation		41,694,000		+34,000
f. Increased cost of centrally furnished services		35,100,000		+1,443,000
g. Increased cost of FTS		---		+16,000
h. Increased cost of Service and Supply Fund		---		+609,000
i. Increased cost of laboratory supplies, materials, and other expenses		117,137,000		+2,889,000
Subtotal				+6,187,000
2. Research management and support:				
a. Within grade increases		27,499,000		+386,000
b. One less day of pay		27,499,000		-103,000
c. Annualization of January 1994 locality pay raise		27,499,000		+205,000
d. January 1995 pay raise		27,499,000		+330,000
e. Increase in unemployment compensation		27,499,000		+9,000
f. Increased cost of centrally furnished services		5,475,000		+224,000
g. Increased cost of FTS		---		+5,000
h. Increased cost of Service and Supply Fund		---		+157,000

Summary of Changes--continued

i. Increased cost of laboratory supplies, materials, and other expenses	54,395,000	+1,424,000
j. DHHS Working Capital Fund	---	+5,000
Subtotal		+2,642,000
Subtotal		+8,829,000

	No.	Amount	No.	Amount
B. Program:				
1. Research projects grants:				
a. Noncompeting	1024	$379,675,000	+156	+$99,667,000
b. Competing	598	190,366,000	-185	-54,451,000
Total	1622	570,041,000	-29	+45,216,000
2. Research centers	45	118,827,000	--	+6,779,000
3. Other research	206	41,589,000	--	-44,000
4. Research training	732	19,466,000	--	+316,000
5. Research and development contracts	337	269,822,000	+16	+18,732,000
6. Intramural research		193,931,000		-1,721,000
7. Research management and support		87,369,000		-100,000
Subtotal, program				+69,178,000
Total changes				+78,007,000

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of AIDS Research

FY 1995 Congressional Justification

	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
NCI	$173,029,000	$213,457,000	$222,712,000
NHLBI	48,058,000	54,977,000	57,910,000
NIDR	8,375,000	11,431,000	12,097,000
NIDDK	6,446,000	10,438,000	11,047,000
NINDS	18,416,000	22,105,000	23,291,000
NIAID	459,698,000	544,791,000	578,109,000
NIGMS	16,850,000	23,945,000	25,409,000
NICHD	38,807,000	56,426,000	64,155,000
NEI	6,283,000	8,381,000	8,870,000
NIEHS	4,272,000	5,608,000	5,903,000
NIA	1,153,000	1,664,000	1,723,000
NIAMS	1,760,000	2,795,000	2,958,000
NIDCD	618,000	1,507,000	1,560,000
NIMH	78,433,000	87,182,000	92,704,000
NIDA	127,047,000	143,376,000	151,733,000
NIAAA	6,823,000	9,457,000	10,000,000
NINR	2,966,000	4,444,000	4,702,000
NCRR	50,881,000	61,383,000	64,960,000
FIC	5,684,000	8,852,000	9,357,000
Subtotal	1,055,599,000	1,272,219,000	1,349,200,000
NLM	1,101,000	3,082,000	3,191,000
OD	14,757,000	25,744,000	26,661,000
B&F	---	---	---
TOTAL	1,071,457,000	1,301,045,000	1,379,052,000

DHHS-NATIONAL INSTITUTES OF HEALTH

Budget Authority by Functional Category

Category	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
I. BASIC SCIENCE RESEARCH:			
A. Biomedical Research:			
1. HIV and HIV genome	$81,701,000	$106,796,000	$114,399,000
2. Immunology	101,910,000	125,877,000	136,287,000
3. Blood/Blood products	6,658,000	14,840,000	14,806,000
4. Diagnostic methods/reagents develop	9,994,000	9,508,000	9,962,000
5. Animal models and related studies	33,281,000	37,403,000	39,507,000
SUBTOTAL, Biomedical Research	233,544,000	294,424,000	314,961,000
B. Neuroscience and Neuropsychiatric Research	49,727,000	58,195,000	61,404,000
C. Behavioral Research:			
1. Mechanisms of behavior and behavior change	21,960,000	31,744,000	36,110,000
2. Prevention of high-risk behaviors	110,833,000	125,803,000	136,754,000
SUBTOTAL, Behavioral Research	132,793,000	157,547,000	172,864,000
D. Therapeutic Agents:			
1. Development	143,013,000	183,782,000	197,913,000
2. Clinical Trials	249,248,000	296,893,000	305,808,000
SUBTOTAL, Therapeutic Agents	392,261,000	480,675,000	503,721,000
E. Vaccines:			
1. Development	65,829,000	84,368,000	89,874,000
2. Clinical Trials	19,040,000	23,623,000	25,068,000
SUBTOTAL, Vaccines	84,869,000	107,991,000	114,942,000

Category	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
F. Research Enhancement:			
1. Training	17,995,000	23,891,000	24,379,000
2. Construction (Extramural)	5,000	6,000	7,000
SUBTOTAL, Research Enhancement	18,000,000	23,897,000	24,386,000
TOTAL, BASIC SCIENCE RESEARCH	911,194,000	1,122,729,000	1,192,278,000
II. RISK ASSESSMENT AND PREVENTION:			
A. Surveillance:			
1. Diseases associated with HIV	6,668,000	3,441,000	3,581,000
2. HIV surveys (incidence, prevalance)	1,701,000	1,700,000	1,000,000
3. Knowledge, attitudes, behaviors	1,983,000	2,633,000	1,340,000
SUBTOTAL, Surveillance	10,352,000	7,774,000	5,921,000
B. Population-Based Research: Natural History, Transmission, Risk Factors:			
1. Transmission:			
a. Sexual	24,278,000	26,866,000	32,576,000
b. Intravenous drug abusers	1,463,000	2,194,000	1,743,000
c. Hemophilia populations	5,420,000	2,061,000	2,153,000
d. Blood recipient/donor studies	6,419,000	7,615,000	7,097,000
e. Perinatal infection	30,859,000	32,899,000	34,709,000
f. Occupationally related	67,000	102,000	110,000
g. Other/Miscellaneous	5,405,000	6,625,000	6,899,000
SUBTOTAL, Transmission	73,911,000	78,362,000	85,287,000
2. Natural history and cofactors	66,675,000	78,910,000	82,279,000
SUBTOTAL, Population based research	140,586,000	157,272,000	167,566,000

Category	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
C. Information and Education/Preventive Services:			
1. High risk or infected persons:			
a. Health education/risk education...........	685,000	565,000	582,000
b. Counseling, testing, partner notification..	198,000	205,000	212,000
c. Perinatal AIDS prevention projects.........	---	---	---
d. HIV prevention among drug abusers..........	1,991,000	2,300,000	2,000,000
e. Special projects:			
(1) Conference of Mayors.................	---	---	---
(2) HIV-related tuberculosis demonstration projects...........................	---	---	---
(3) National Hemophilia AIDS/HIV prevention project..................	---	---	---
(4) Community-based demonstration projects	---	---	---
SUBTOTAL, Special projects..........			
SUBTOTAL, High-Risk or Infected Persons......	2,874,000	3,070,000	2,794,000
2. Special Minority Initiatives..................	391,000	431,000	457,000
3. School and college aged youth:			
a. National efforts..........................	---	---	---
b. State and local projects..................	---	---	---
c. Program development and training..........	1,000	1,000	---
SUBTOTAL, School and college aged youth....	1,000	1,000	---
4. General Public and Special Programs:			
a. National:			
(1) Clearinghouse.......................	---	---	---
(2) Hotline (general public).............	---	---	---
(3) Treatment trials and therapy, information services................	1,686,000	4,832,000	5,169,000
SUBTOTAL, National.................	1,686,000	4,832,000	5,169,000

Category	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
b. Regional, state, and local	131,000	748,000	543,000
SUBTOTAL, Gen. Pub. and Spec. Prog	1,817,000	5,580,000	5,712,000
5. Health-Care Workers and Providers:			
a. Education and training centers	706,000	741,000	725,000
b. Other types of training	426,000	447,000	448,000
SUBTOTAL, Health-Care Workers and Providers	1,132,000	1,188,000	1,173,000
6. Prevention Capacity Enhancement	---	---	---
SUBTOTAL, Information and education/preventive services	6,215,000	10,270,000	10,136,000
TOTAL, RISK ASSESSMENT AND PREVENTION	157,153,000	175,316,000	183,623,000
IV. Clinical Health Services Research and Delivery:			
A. Services	---	---	---
B. Health Services Grants	---	---	---
C. Construction	---	---	---
D. Research	3,110,000	3,000,000	3,151,000
TOTAL, CLINICAL HLTH SERV. RESCH AND DEL	3,110,000	3,000,000	3,151,000
V. PHS-Wide Activities:			
A. OASH/NAPO	---	---	---
C. Construction (PHS Faciltites)	---	---	---
TOTAL	1,071,457,000	1,301,045,000	1,379,052,000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Office of AIDS Reserch

Budget Authority by the Plan

	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
I. Natural History and Epidemiology:			
Objective 1	$45,299,000	$50,020,000	$51,238,000
Objective 2	62,758,000	79,068,000	87,579,000
Objective 3	37,929,000	43,024,000	45,540,000
Objective 4	16,527,000	22,378,000	22,702,000
Total, Natural History and Epidemiology	162,513,000	194,490,000	207,059,000
II. Etiology and Pathogenesis:			
Objective 1	134,660,000	155,617,000	165,987,000
Objective 2	24,891,000	27,727,000	27,495,000
Objective 3	14,014,000	16,307,000	17,628,000
Objective 4	34,994,000	40,241,000	42,868,000
Objective 5	12,638,000	14,136,000	15,060,000
Objective 6	6,879,000	8,455,000	9,050,000
Total, Etiology and Pathogenesis	228,076,000	262,483,000	278,088,000
III. Therapeutics:			
Objective 1	74,221,000	94,771,000	100,872,000
Objective 2	109,930,000	132,435,000	136,902,000
Objective 3	60,561,000	74,846,000	80,208,000
Objective 4	24,802,000	30,989,000	32,434,000
Objective 5	30,301,000	41,974,000	45,536,000
Objective 6	18,655,000	25,513,000	26,712,000
Objective 7	111,991,000	123,359,000	127,057,000
Objective 8	931,000	892,000	1,072,000
Total, Therapeutics	431,392,000	524,779,000	550,793,000
IV. Vaccines:			
Objective 1	56,630,000	71,647,000	76,378,000
Objective 2	9,968,000	11,380,000	12,018,000
Objective 3	14,946,000	21,593,000	22,954,000
Total, Vaccines	81,544,000	104,620,000	111,350,000

Budget Authority by the Plan--continued

	FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate
V. Behavioral Research:			
Objective 1	66,807,000	79,345,000	87,874,000
Objective 2	44,884,000	51,673,000	56,768,000
Objective 3	24,973,000	28,097,000	30,611,000
Total, Behavioral Research	136,664,000	159,115,000	175,253,000
VI. Training and Infrastructure:			
Objective 1	14,772,000	19,905,000	20,183,000
Objective 2	11,468,000	17,940,000	18,596,000
Total, Training and Infrastructure	26,240,000	37,845,000	38,779,000
VII. Information Dissemination:			
Objective 1	5,028,000	7,713,000	7,730,000
Total, Information Dissemination	5,028,000	7,713,000	7,730,000
Director's Discretionary Fund	---	10,000,000	10,000,000
Total funding by the Plan	1,071,457,000	1,301,045,000	1,379,052,000

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of AIDS Research

FY 1995 Commitment Base

	Extramural	Intramural	Research Management and Support	Total 1/
NCI	$96,141,000	$100,755,000	$7,643,000	$204,539,000
NHLBI	44,136,000	4,766,000	1,743,000	50,645,000
NIDR	7,025,000	3,330,000	241,000	10,596,000
NIDDK	7,935,000	1,288,000	---	9,223,000
NINDS	11,389,000	5,268,000	26,000	16,683,000
NIAID	414,928,000	58,915,000	33,020,000	506,863,000
NIGMS	22,207,000	---	109,000	22,316,000
NICHD	47,084,000	3,006,000	3,397,000	53,487,000
NEI	6,587,000	1,352,000	193,000	8,132,000
NIEHS	3,938,000	1,369,000	---	5,307,000
NIA	825,000	692,000	---	1,517,000
NIAMS	1,563,000	761,000	434,000	2,758,000
NIDCD	1,440,000	---	137,000	1,577,000
NIMH	65,362,000	8,995,000	4,627,000	78,984,000
NIDA	117,595,000	5,349,000	5,637,000	128,581,000
NIAAA	6,616,000	732,000	333,000	7,681,000
NINR	3,280,000	761,000	112,000	4,153,000
NCRR	62,088,000	---	1,390,000	63,478,000
FIC	8,217,000	---	887,000	9,104,000
Subtotal	928,356,000	197,339,000	59,929,000	1,185,624,000
NLM	---	---	3,170,000	3,170,000
OD	---	---	26,472,000	26,472,000
B&F	---	---	---	---
TOTAL	928,356,000	197,339,000	89,571,000	1,215,266,000

1/ This is the estimate of the total commitments based on the FY 1994 Appropriation and does not necessarily reflect the amount that will be transferred to the ICDs within 15 days of the appropriation.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Budget Authority by Object

		FY 1994 Appropriation	FY 1995 Estimate	Increase/ Decrease
	Personnel Compensation:			
11.1	Full-time permanent	$39,817,000	$40,467,000	+$650,000
11.3	Other than full-time permanent	11,714,000	11,844,000	+130,000
11.5	Other personnel compensation	2,086,000	2,089,000	+3,000
11.8	Special personal services payments	4,552,000	4,566,000	+14,000
11.9	Total, Personnel Compensation	58,169,000	58,966,000	+797,000
12.1	Civilian personnel benefits	12,924,000	13,283,000	+359,000
13.0	Benefits or former personnel			
21.0	Travel and transportation of persons	2,636,000	2,847,000	+211,000
22.0	Transportation of things	431,000	432,000	+1,000
23.1	Rental payment to GSA	1,572,000	1,643,000	+71,000
23.2	Rental payments to others	669,000	757,000	+88,000
23.3	Communications, utilities, and miscellaneous charges	3,268,000	3,653,000	+385,000
24.0	Printing and reproduction	1,174,000	1,112,000	-62,000
25.1	Consulting services	5,301,000	5,349,000	+48,000
25.2	Other services	88,724,000	90,964,000	+2,240,000
25.3	Purchases from govt. accts	71,488,000	73,651,000	+2,163,000
25.4	Operation of GOCOs	7,106,000	7,116,000	+10,000
25.5	Research and development contracts	262,974,000	276,954,000	+13,980,000
26.0	Supplies and materials	23,898,000	24,589,000	+691,000
31.0	Equipment	9,975,000	9,733,000	-242,000
32.0	Land and structures	---	---	
41.0	Grants, subsidies, and contributions	750,736,000	808,003,000	+57,267,000
42.0	Insurance claims and indemnities			
43.0	Interest and dividends			
99.9	Total budget authority	1,301,045,000	1,379,052,000	+78,007,000

National Institutes of Health
Administrative Costs
Budget Authority
OAR

	Object Classification	FY 1994 Appropriation	FY 1994 Estimate Comparable To FY 1995	FY 1995 Estimate	Change From FY 1994 Comparable
	Personnel Compensation:				
11.1	Full-time permanent	39,817	39,817	40,467	650
11.3	Other than full-time permanent	11,714	11,714	11,844	130
11.5	Other personnel compensation	2,086	2,086	2,089	3
11.8	Special personnel services payments	4,552	4,552	4,566	14
11.9	Subtotal, personnel compensation	58,169	58,169	58,966	797
12.1	Civilian personnel benefits	12,924	12,924	13,283	359
13.0	Benefits for former personnel	0	0	0	0
	Subtotal Pay Costs	71,093	71,093	72,249	1,156
21.0	Travel and transportation of persons	3,208	2,636	2,847	211
22.0	Transportation of things	435	431	432	1
23.2	Rental payments to others	758	669	757	88
23.3	Communications, utilities, and miscellaneous charges	3,506	3,268	3,653	385
24.0	Printing and reproduction	1,773	1,174	1,112	(62)
25.0	Other Services	165,065	152,613	157,135	4,522
26.0	Supplies and materials	31,353	24,257	24,953	696
	Subtotal non-pay costs	206,098	185,048	190,889	5,841
	Total Administrative Costs	277,191	256,141	263,138	6,997

NOTE: FY 1994 does not include rescission and FY 1995 does not include any amendments.

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NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1994 Amount Authorized	1994 Appropriation	1995 Amount Authorized	1995 Budget Request
Research and Investigation..	Title IV Section 301		Indefinite	$1,271,579,000	Indefinite	$1,359,270,000
Office of AIDS Research.......	Title XXIII Section 2351			---		
Emergency Discretionary Fund...	Title XXIII Section 2356		$100,000,000	10,000,000	$100,000,000	10,000,000
National Research Service Awards..	Section 487(d)		400,000,000	19,466,000	Such sums as necessary	19,782,000
				1,301,045,000		1,379,052,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Appropriation History

Year	Budget Estimate 1/ to Congress	House Allowance	Senate Allowance	Appropriation
1995	$1,379,052,000			

1/ Includes all amounts associated with the National Institutes of Health AIDS Research Program.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

Budget Authority 1/
(Dollars in thousands)

FY 1991	$1,012,469
FY 1992	1,047,456
FY 1993	1,071,457
FY 1994	1,301,045
FY 1995	1,379,052

1/ The budget authority prior to FY 1992 was developed by adding the total obligations from NIMH, NIDA, NIAAA and ADAMHA B&F ($1,600) to the NIH budget authority.

Note: FTEs associated with HIV/AIDS Research Activities are found in the Institutes, Centers, and Divsions.

Justification

Office of AIDS Research

FY 1993 Actual	FY 1994 Appropriation	FY 1995 Estimate	Increase or Decrease
$1,071,457,000	$1,301,045,000	$1,379,052,000	+$78,007,000

General Statement

The NIH Office of AIDS Research (OAR) was established in April 1988 and was authorized later that year in Public Law 100-607, the Health Omnibus Programs Extensions Act. The OAR, in the Office of the Director, NIH, is responsible for coordination of the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Such policy issues include legal and ethical considerations as well as issues of laboratory safety. Through participation in PHS and NIH committees, the OAR has increased its efforts to improve cross-PHS and cross-NIH coordination and collaboration of AIDS related research. Special attention has been given to improving the dissemination of AIDS-related information to ensure that research findings are rapidly incorporated into treatment guidelines used by health care providers.

In June of 1993, the President signed the NIH Revitalization Act of 1993. With the passage of this Act the OAR was required to develop a comprehensive plan for NIH AIDS-related research activities which must be updated annually. The Plan will be the basis for distribution and disbursement of appropriated AIDS-related research funds to the Institutes, Centers, and Divisions (ICDs) within NIH.

The OAR has developed a comprehensive research plan entitled--*The National Institutes of Health Plan for HIV-Related Research*--establishing objectives, priorities, and policy statements governing the conduct and support of all NIH AIDS-related research activities in the areas of Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral Research, Training and Infrastructure, and Information Dissemination. The Plan is the result of more than a year of work spearheaded by the OAR. To develop the plan, the OAR consulted with, and received guidance from the NIH AIDS Program Advisory Committee as well as the NIH Institute and Center Directors, AIDS Coordinators, and planning officers as well as outside researchers, clinicians, and community advocates. The expertise of many of the scientists in the intramural and extramural programs of each Institute was also solicited. All of these experts assisted the OAR in establishing the Plan's overall scientific objectives and strategies and in determining their priority.

As the Plan demonstrates, HIV-related research spans nearly every area of scientific endeavor. The Plan provides a clear picture of the current scientific opportunities in HIV research, the scientific gaps that remain, and the existing comprehensive nature of the NIH AIDS-related research program.

The overall NIH AIDS research program reflects and responds to the changing demographics of the pandemic, specifically in regard to the increasing incidence of HIV infection in women, children, adolescents, injection drug users (IDUs) and minority populations in the United States. The complex research issues affecting these populations intersect all NIH scientific disciplines.

Community representatives of HIV-infected and affected individuals serve on NIH AIDS advisory groups, participate in the design of research protocols, and evaluate NIH programs. Community-based physicians conduct research and clinical trials in accessible settings. The HIV-infected and affected communities have become partners in NIH research efforts and continue to be involved.

The *NIH Plan for HIV-Related Research* is an evolving, working document, a research framework for annual review, updating, and modification, which will reflect the ever-changing scientific opportunities, scientific priorities, and challenges of the HIV pandemic here in the United States and around the world.

The authorizing legislation states that the Comprehensive Plan must be established and in place one year before funds can be appropriated in accordance with the Plan. The Plan was finalized and presented to the Secretary, DHHS in September, 1993 and forwarded to Congress. As a result of these actions the FY 1995 budget has been developed in accordance with the Comprehensive Plan for HIV-Related Research.

Furthermore, the legislation states that the Director, OAR shall receive all funds available for AIDS activities of the NIH. In following the intent of the legislation, a separate appropriation is proposed for the Director, OAR with transfer authority to provide the funds to the ICDs for their AIDS-related research activities. It was felt that the transfer authority would provide the Director, OAR the vehicle to "allocate" the funds to the ICDs in the required 15 days for ongoing research activities and 30 days for new and competing research activities.

In the past, each ICD retained within their appropriation accounts all funds associated with their AIDS research portfolios, but with the passage of the Revitalization Act, the funds will be appropriated directly to the Director, OAR for distribution to the ICDs using a new transfer authority. This will provide the Director, OAR the ability to promote a comprehensive approach to AIDS-related research at NIH while maintaining the scientific expertise available in each of the ICDs. By providing the monies to the ICDs in this manner, it will allow the ICDs to continue their research programs without disruption to the overall scientific mission of their Institute. Alternatives to this approach were considered by NIH, PHS and DHHS, i.e. intraagency agreements or direct allotments; however, it was felt that within current procedures, the transfer authority would be the most appropriate and expeditious manner to provide funds to the ICDs in the time frame stipulated, and most directly and clearly responds to the provisions of the NIH Revitalization Act.

To foster cross-NIH collaboration and participation, the OAR provides funding support to scientific research opportunities in the ICDs as well as for meetings and other necessary research-related activities. In FY 1995, the OAR Discretionary (Research Development) Fund will provide monies to support or provide supplemental support to ICD peer-reviewed grant applications and contracts submitted in response to Request for Applications, Request for Proposals, and Program Announcements. This allows expeditious pilot funding for new scientific initiatives as well as for scientific "break-throughs" or emergent projects in ongoing research identified subsequent to the traditional budget process. In addition, OAR funds will be used to support AIDS-related multidisciplinary meetings, which serve to promote coordination and collaboration between and among the ICDs.

In FY 1994, the OAR established five coordinating committees that will cover each of the major program areas of the *NIH Plan for HIV-Related Research:* Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral Research. The committees will meet on a regular basis to share research information, discuss ongoing activities, and promote collaborative efforts. The committees will serve to annually review and make recommendations on research priorities for inclusion into the *NIH Plan for HIV-Related Research.* Coordinating committees will recommend to the Director, OAR and the Office of AIDS Research Advisory Council (OARAC) expenditures from the OAR Discretionary Fund and identify scientific opportunities in the research effort, both intramural and extramural.

The OAR established the OARAC in FY 1994. The council will meet at least three times a year and its responsibilities will include advising the Director, OAR on scientific research program priorities and scientific opportunities. The Council will actively participate in the development of the annual NIH AIDS budget and will be required to act on staff and coordinating committee recommendations for expenditures from the newly authorized OAR Discretionary Fund.

The OAR fosters and develops plans for NIH involvement in international AIDS-related research activities. The OAR has worked closely with FIC and the ICDs to coordinate international AIDS programs. The public health urgency of AIDS-related research and the need to disseminate research findings with immediate clinical relevance require particular attention. The OAR's Regional Technology Transfer (RTT) Program concentrates on the translation of clinical results into the training of health care providers in state-of-the-art treatment. To date, the OAR has planned over 13 RTT conferences nationwide with special emphasis in geographic areas with increasing numbers of HIV-infected underrepresented populations.

The NIH has played a key role in characterizing the virus and combatting the disease. In accordance with the NIH mission to conduct and support biomedical and behavioral research on the causes, diagnosis, prevention, and cure of diseases, the NIH has established a comprehensive program of basic and clinical research on HIV infection and its sequelae. In support of HIV-related research, the NIH provides for the training of personnel and the development of other research resources, such as animal models, and construction of research facilities. As part of its mandate to direct programs for the collection, dissemination, and exchange of scientific information, the NIH has developed systems for dissemination of information on AIDS-related biomedical and behavioral research, particularly the AIDS clinical trials program.

The NIH HIV-related research effort can be divided into five major scientific categories: (1) natural history and epidemiology, (2) etiology and pathogenesis, (3) therapeutics, (4) vaccines, and (5) behavioral research. These scientific areas, while defined separately, are linked together and form stepping stones to each other. The basic scientific foundation of etiology and pathogenesis is necessary for defining the natural history of the disease as well as for the development and evaluation of potential drugs and vaccines. In addition, research resources are divided into two areas of emphasis: training and infrastructure and information dissemination. An explanation of these areas follows.

Areas of Emphasis

Natural History and Epidemiology

In the research area of Natural History and Epidemiology the FY 1995 Request is $207,059,000 an increase of $12,569,000 or 6.5 percent over the FY 1994 Estimate amount of $194,490,000. The NIH performs epidemiologic research that is complimentary to that of the Centers for Disease Control and Prevention in prospectively studying cohorts of HIV-infected individuals and uninfected individuals who are at risk of infection. The NIH is conducting a number of epidemiologic studies to examine the natural history of HIV infection and the effects of viral factors, host factors, cofactors, and therapeutic and prophylactic interventions on the risk of infection and diseases progression. This research is performed in the United States as well as in other countries that may exhibit different patterns of the pandemic. Such studies provide unique opportunities to identify risk factors, to understand the natural history of HIV infection, and to identify populations suitable for participation in future domestic and international HIV vaccine efficacy trials. Examples of such research include the study of sexual transmission in specific populations; the study of the natural history of HIV-related disease in women, men, adolescents, children, minorities, and IDUs; the study of perinatal transmission; and the study of behavior related to the risk of HIV transmission.

Etiology and Pathogenesis

In the research area of etiology and pathogenesis the FY 1995 Request is $278,088,000 an increase of $15,605,000 or 5.9 percent over the FY 1994 Estimate amount of $262,483,000. Efforts to combat HIV infection are based on developing an understanding of the HIV life cycle through elucidation of the mechanisms of infection, viral activation and expression, and immunosuppression. Examples of such research include the isolation and cloning of HIV and the sequencing and delineation of the function of HIV genes. Also included in the category of pathogenesis are basic and clinical research on the disease progression, HIV-related malignancies, HIV-associated opportunistic infections, neuropsychological and neuropsychiatric sequelae, and other sequelae such as wasting and endocrine disorders as well as research on the mechanisms by which cofactors may influence disease progression. The NIH also focuses efforts on improving the understanding of the progression of disease and clinical manifestations in women, children, adolescents, minorities, and IDUs. The development of improved diagnostics for HIV infection and its associated opportunistic infections and the development of appropriate animal models are crucial.

Therapeutics

In the research area of therapeutics the FY 1995 Request is $550,793,000 an increase of $26,014,000 or 4.9 percent over the FY 1994 Estimate amount of $524,779,000. NIH-sponsored studies are actively pursuing the discovery and development of potential therapies for the prophylaxis, early intervention, and treatment of HIV infection and its sequelae. Two approaches are being taken for the identification of potential antiretroviral agents, including targeted drug development that utilizes structural biology techniques specifically to design drugs that interfere at various stages of the HIV life cycle, and drug screening of synthetic and natural products for anti-HIV activity. The NIH sponsors intramural and extramural clinical trials of these potential therapeutic agents in single or multidrug regimens to demonstrate drug safety and efficacy for the control and treatment of HIV infection and its accompanying opportunistic infections and malignancies in individuals of all ages. The development and evaluation of immune based therapies to restore the immune system in HIV-infected individuals is a priority.

Vaccines

In the research area of vaccines the FY 1995 Request is $111,350,000 an increase of $6,730,000 or 6.4 percent over the FY 1994 Estimate amount of $104,620,000. The discovery and development of safe and effective AIDS vaccines are based on basic biomedical research on HIV. Vaccine candidates are being evaluated for prevention of HIV transmission, including transmission via the maternal-fetal route of infection, and for treatment of HIV-infected individuals as immune modulators and immune enhancers. Preclinical evaluation of vaccine candidates involves testing in primate and non-primate animal models for demonstration of safety and efficacy. Current vaccine candidates under development include whole killed virus, purified viral products, synthetic viral peptides, recombinant products, genetic recombinant viruses, and anti-idiotypic antibodies. Vaccine discovery and development are closely coordinated with international epidemiology studies to identify genetic variations of HIV that may affect the development of potential AIDS vaccines and to identify populations suitable for future vaccine efficacy clinical trials. In addition, strategies are being developed to increase adherence to study protocols in future clinical trials.

Behavioral Research

In the research area of behavioral research the FY 1995 Request is $175,253,000 an increase of $16,138,000 or 10.1 percent over the FY 1994 Estimate amount of $159,115,000. The NIH conducts basic research on behavior and the means of motivating and sustaining behavior change, providing information on the influence of behaviors associated with the transmission of HIV by elucidating the nature and extent of at risk behaviors. These efforts provide information that is relevant to the design of intervention programs aimed at reducing HIV transmission through identifying effective approaches to modifying behaviors and sustaining behavior change, identifying cultural barriers to behavior change, and identifying populations resistant to behavior intervention. The NIH supports a multisite, multipopulation intervention study to evaluate prevention strategies. Some studies are international in scope, including a collaborative effort between the NIH and the U.S. Agency for International Development with the goal of collecting information in support of the development of behavioral intervention strategies. Studies in other areas of behavioral research are determining how HIV-infected individuals are perceived and how individuals and their families respond to and cope with the disease and its manifestations. Behavioral research also is crucial for the HIV vaccine and therapeutics research efforts.

Training and Infrastructure

In the area of training and infrastructure the FY 1995 Request is $38,779,000 and increase of $934,000 or 2.4 percent over the FY 1994 Estimate amount of $37,845,000. The NIH supports a number of intramural and extramural research resource programs. Included in these programs are grants for training researchers, developing animal models, and constructing or improving existing facilities and equipment to conduct AIDS-related research.

Information Dissemination

In the area of information dissemination the FY 1995 Request is $7,730,000 an increase of $17,000 or .2 percent over the FY 1994 Estimate amount of $7,713,000. The NIH has addressed the important need for information dissemination in a number of arenas. Information on standards-of-care requires coordination among various agencies of the Public Health Service (PHS) as well as outside organizations. The NIH supports a number of computerized databases as well as mechanisms such as the "Clinical Alerts" to rapidly disseminate crucial clinical trials results to health care professionals.

Following are the Areas of Emphasis with their FY 1995 objectives.

I. Natural History and Epidemiology

1. Delineate the epidemiology of HIV infection in those populations in which the pandemic is increasing, such as women, children, adolescents, minorities, and injection drug users (IDUs)

2. Delineate the natural history (including transmission) of HIV infection in women, children, minorities, adolescents, and IDUs

3. Elucidate the natural history (including transmission) of HIV infection and AIDS in pregnant women and their infants

4. Further ensure the safety of the blood supply

II. Etiology and Pathogenesis

1. Delineate the cellular and molecular mechanisms underlying the immune dysfunction associated with HIV infection

2. Elucidate the pathogenesis of HIV-related malignancies

3. Elucidate the pathogenesis of certain AIDS-related opportunistic infections

4. Elucidate the pathogenic mechanisms involved in central nervous system impairment and HIV-associated encephalopathy and AIDS-related dementia complex

5. Elucidate the pathogenic mechanisms that may be unique in special populations, such as women, children, and adolescents with HIV infection

6. Elucidate the pathogenic mechanisms involved in other syndromes associated with HIV infection, such as wasting, autoimmune diseases, endocrine disorders, and other organ-specific dysfunctions

III. Therapeutics

1. Continue screening, discovery, and development of therapeutic agents that demonstrate activity against retroviruses

2. Continue and enhance clinical trials of agents against HIV

3. Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated opportunistic infections (OIs), including those specific to women and children

4. Continue screening, discovery, and development of therapeutic agents that demonstrate activity against HIV-associated malignancies and bring the most promising of the new drugs into clinical trials

5. Accelerate the development and clinical testing of strategies that enhance and/or restore the suppressed immune systems of HIV-infected individuals

6. Develop therapies for treating and preventing central nervous system (CNS) impairment and AIDS dementia complex (ADC)

7. Increase participation of urban poor, minorities, women of child-bearing age, children, adolescents, IDUs, and individuals residing in rural areas in clinical trials

8. Develop clinical trials for the treatment of other HIV-related dysfunctional states, including endocrine dysfunction, wasting syndrome, and other syndromes

IV. Vaccines

1. Strengthen the science base necessary for the development of a safe and effective vaccine(s) against HIV infection

2. Develop the infrastructure and pursue the appropriate natural history and epidemiologic studies in order to determine the populations in whom vaccine trials would be likely to establish the safety and efficacy of vaccine candidates

3. Conduct clinical trials, when appropriate, on promising vaccine candidates in order to establish their safety and efficacy

V. Behavioral Research

1. Determine the spectrum, frequency, and determinants of sexual behaviors, drug and alcohol use, and other behaviors associated with risk of HIV transmission and disease progression in order to develop effective interventions

2. Determine and improve the efficacy of psychosocial/behavioral and pharmacological treatment interventions for drug dependency and determine the role, if any, these play in inhibiting the spread of HIV infection among populations who are dependent on drugs

3. Study the behavioral and social consequences of AIDS and HIV infection across the life course, including quality of life, family issues, and health care worker interventions

VI. Training and Infrastructure

1. Provide both domestic and international training in biomedical and behavioral research on HIV

2. Establish appropriate infrastructure for the conduct of HIV research domestically and internationally

VII. Information Dissemination

1. Expedite the dissemination of the latest information on state-of-the-art therapies, health care, and prevention techniques to domestic as well as international audiences as appropriate

AREA OF EMPHASIS:

Natural History and Epidemiology

Surveillance has shown the demographics of HIV infection and AIDS in the United States changing from an illness initially affecting homosexual and bisexual men to the current pandemic with increasing rates of infection among women, children, adolescents, minorities, and drug users. The NIH conducts a number of studies on the natural history of HIV infection and opportunistic infections (OIs) and malignancies as well as the effects of viral factors, host factors, and cofactors on the risk of infection and disease progression. Cohorts of HIV-infected individuals and uninfected individuals at risk of infection are followed in clinical epidemiology studies at domestic and international sites.

International epidemiology studies sponsored by the NIH contribute significantly to the understanding of the transmission, natural history, and risk factors associated with HIV infection. NIH-sponsored collaborative epidemiology research activities, such as the Preparation for HIV/AIDS Vaccine Evaluations (PAVE) programs, foster the development of research skills and infrastructure in countries where HIV infection is epidemic. These resources will be crucial for future international HIV vaccine efficacy trials.

NIH-sponsored epidemiological studies delineate the biological mechanism underlying possible host immunity to HIV infection among at-risk uninfected cohorts. These programs will maintain and expand their data collection, data processing, and data analysis capabilities. NIH also will continue monitoring HIV infection among injection drug users (IDUs) and their sexual partners. These programs will provide information necessary for the development of models for AIDS prevention programs that are integrated with mental services, primary health care, and TB surveillance. Similarly, the NIH will support the development of effective prevention interventions for specific risk behaviors among various at-risk populations.

NIH also will continue supporting cross-sectional epidemiologic studies of men, women, and adolescents at risk of HIV infection through IDU and heterosexual transmission. The data obtained from these studies may provide useful information in defining determinants of male-female differences with respect to HIV infection and disease progression. New efforts will include studies on: biological factors that affect infectivity of the virus in vaginal, seminal, and other body fluids; comparisons of cell-free and cell-associated virus in body fluids; clinical correlates of disease progression; and the role of other cofactors.

Recent analysis of the Multicenter AIDS Cohort Study has identified a group of "long-term survivors" whose CD+4 counts have not declined despite their being HIV infected for seven or more years. Further investigation of this group of men will be undertaken to explore the immune responses to HIV that have occurred in this group which may be directly applicable in the development of therapeutic regimens.

Natural History of HIV Infection

The NIH Surveillance, Epidemiology, and End Results (SEER) program has demonstrated a striking increase in the incidence of non-Hodgkin's lymphoma (NHL) in HIV-infected patients receiving protracted antiviral therapy. NHL develops in approximately 10 percent of AIDS patients treated with dideoxynucleosides. It is expected that the number of HIV-associated malignancies will continue to increase as the life expectancy of HIV-infected patients is prolonged by antiviral treatment.

NIH plans to establish a multi-state AIDS/cancer match registry that will link AIDS and cancer registries in 15 sites. The establishment of an AIDS/cancer match registry will provide an important framework for determining the effects of HIV as a cofactor in the development of diverse malignancies.

Another striking phenomenon has been the increase in tuberculosis (TB) and multidrug-resistant TB related to HIV infection in certain domestic and international populations. NIH will support research to determine risk factors for active pulmonary TB in HIV-infected and uninfected persons with the goal of identifying potential public health interventions. The studies will investigate all major clinical manifestations of TB, the host protective immune response against TB, and the immune mechanisms responsible for lung damage associated with TB.

HIV Infection in Women

While women experience most of the clinical manifestations of HIV infection that occur in men, they also experience some that are unique to women as well as some that are more prevalent in women, such as esophageal candidiasis and chronic herpes simplex infections. The Women's Interagency HIV Study (WIHS), conducted in collaboration with other PHS agencies, will identify the nature and rate of HIV disease progression in women, identify and characterize manifestations of HIV specific to women, and assess the effects of therapeutic regimens on the health and survival of HIV-infected women.

NIH has implemented a program to assess clinical and psychosocial features of HIV infection in teenagers and young adults in order to determine appropriate treatment and prevention strategies. In addition to defining the predictive value of various immunologic parameters in this age group, this study will investigate the influence of a changing hormonal milieu on immune function.

There also is a high incidence of HIV-associated cervical cancer, which has proved to be rapidly progressive and refractory to therapy. SEER has established a Special Surveillance Study to define more closely the incidence and spectrum of histopathology of cervical cancer in HIV-infected women. Coinfection with human papillomavirus (HPV) is common in women with HIV. HPV and HIV have been shown to act synergistically to increase expression of individual viral genes. The enhanced expression of viral proteins increases viral replication, abrogates host tumor suppressor functions, and further exacerbates cellular immunodeficiency. This research area will be further investigated in FY 1995.

In FY 1995, NIH-sponsored scientists will compare the progression of HPV infection and the evolution to cervical intraepithelial neoplasia (CIN) and cancer in women with different types of immunodeficiency. Additional studies will be conducted to determine the effects of pregnancy, oral contraceptives, coinfections with other STDs, and menopause on susceptibility and disease progression.

Maternal-Fetal Transmission

The NIH continues to study the natural history of HIV infection and AIDS in pregnant women and infants, including the timing, mechanisms, and risk factors of maternal-fetal transmission; the effects of alcohol and illicit drugs on HIV transmission and disease progression; the progression of HIV-related central nervous system disease in infants and children; the impact of HIV infection on childhood diseases such as measles, rubella, and pertussis; and the effect of pregnancy on specific clinical manifestations in the mother. In FY 1995, the NIH will conduct studies on the role of breast feeding in HIV transmission and the role of the placenta in vertical transmission.

A significant new development in the clinical perspective of HIV infection is that more than 90 percent of AIDS patients are coinfected with cytomegalovirus (CMV). Recent evidence suggests that HIV-infected pregnant women are at greater risk for delivering children with congenital CMV infection and that these infected children are more vulnerable to CMV morbidity.

Planned studies will support efforts concerned with the prevalence of HIV antibody in childbearing women. This research involves the development and evaluation of procedures adaptable to microquantities of blood obtained from newborn specimens already being collected for routine newborn screening.

In conjunction with recent NIH-sponsored natural history and epidemiology studies, two assays recently have been identified: a new PCR test to improve the early diagnosis of infants at risk for HIV infection and a rapid and economic test to identify HIV-infected infants and children after the first few months of life.

Recent findings from the Pediatric and Cardiovascular Complications of Vertically Transmitted HIV Infection study indicate that infected pregnant women with normal immune function are more likely to have uninfected babies. The findings from this study will facilitate the planning of additional maternal-infant studies designed to lower the risk of vertical transmission.

Safety of the Blood Supply

NIH supports studies to further ensure the safety of the blood supply. In FY 1995, NIH will initiate a new program focused on the inactivation of transfusion-transmitted viruses in blood and blood components.

AREA OF EMPHASIS:

Etiology and Pathogenesis

NIH-sponsored investigations have led to significant advances in the understanding of HIV and how it causes disease. These studies facilitated the identification of HIV as the causative agent of AIDS, the development of a highly sensitive diagnostic test for HIV infection, the elucidation of the role of the structural and regulatory genes of HIV, and the delineation of HIV cytopathic mechanisms.

Using sophisticated molecular biology techniques, the mechanisms responsible for HIV antigenic variation are being defined, the HIV surface molecules capable of eliciting immune responses are being identified, and the regulatory mechanisms of viral gene expression are being delineated.

Pathogenic Mechanisms of HIV Infection

Ongoing research at the molecular, cellular, and organ-system levels is elucidating the pathogenic mechanisms of HIV infection. Recent studies have shown that newly infected patients experience a high rate of viral replication and that their immune systems undergo changes that continue until the development of AIDS. Research at the cellular and molecular levels also includes studies on the mechanisms by which HIV enters and infects various cell types; the interaction between the viral regulatory elements and infected cells, which appear to maintain a persistent, controlled infection; the mechanisms of viral activation; and the mechanisms related to increased viral expression. Additional studies are exploring the interactions between HIV and other viral infections, interactions between HIV and oncogenes, and interactions between HIV and cellular genes and proteins.

In FY 1995, NIH will provide funding for investigator-initiated research that will focus on delineating the cellular and molecular mechanisms underlying the immune dysfunction associated with HIV infection. A program will be established on the role of dendritic cells in early HIV infection. Dendritic cells, which bind to HIV and activate naive T cells, may be important in the initiation of HIV infection. Elucidation of this process *in vivo* and *in vitro* will further the understanding of HIV pathogenesis.

NIH-funded studies will apply state-of-the-art technologies identify and develop human monoclonal antibodies against specific antigenic regions of HIV. These antibodies may then form the basis of passive immunotherapy for HIV infection.

NIH will expand its research efforts to delineate the pathogenic mechanisms of HIV infection at the molecular level. The studies will be designed to delineate the mechanisms of cytokine-induced regulation of HIV expression in latently or chronically infected cells, to understand the molecular basis for the regulation of HIV gene expression, and to develop new approaches for AIDS vaccine development and evaluation.

Factors Affecting Infectivity and Susceptibility

The biologic determinants of infectivity and susceptibility are important areas currently under investigation. In FY 1995, specific attention will be focused on the possible correlation between the level of cell-free or cell-associated virus in blood, semen, or cervical/vaginal secretions and the probability of transmission.

AIDS-Associated Cancers

Since its recognition, AIDS has had a close association with a broad spectrum of cancers, including Kaposi's sarcoma (KS), lymphomas, basal cell carcinoma, anogenital carcinomas, and hepatitis B-related hepatocellular carcinoma. The types of malignancies and their incidence rates are increasing as the development of effective antiretroviral therapies and prophylaxis against opportunistic infections (OIs) leads to prolonged survival of AIDS patients in the immunodeficient state. NIH investigators have demonstrated the striking relationship between profound cellular immunodeficiency, manifested by the depletion of CD4 lymphocytes, and the development of non-Hodgkin's lymphoma (NHL), particularly when the CD4 count falls below $50/mm^3$. Elucidation of the interactive components involved in the pathogenesis of the various AIDS-associated cancers will translate into clinical trials of multimodal therapies that are designed to interdict the effects of multiple factors.

Over the past few years, more HIV-infected individuals have been developing a particularly aggressive form of NHL known as AIDS lymphoma. The onset of AIDS lymphoma coincides with the phase of profound loss of immune function in HIV-infected patients. Since NHL is a disease of B lymphocytes, the antibody-producing cells of the immune system, NIH is focusing on B-cell immunoregulatory mechanisms in this disease. Recent results have shed light on the mechanism of B-cell lymphoma development, the origin of two important human immunodeficiency diseases, and other facets of basic immunology.

Several therapeutic strategies for B-cell lymphomas are under development. These primarily target the cell-surface antibody of the lymphoma cell, because it is tumor-specific. An alternative approach is to target B-cell molecules that are not tumor-specific but are required for rapid cell division. Early studies with one such molecule, CD20, have been highly encouraging. The discovery of new molecules like CD40 and BPK provides additional targets for this approach. These findings provide the basis for future efforts focused on understanding the basic immunobiology of HIV-associated B-cell lymphomas, and shed light on other B-cell lymphomas.

The NIH Surveillance, Epidemiology, and End Results (SEER) program continues to uncover the emerging profile of AIDS-related malignancies. SEER has established a Special Surveillance Study to define more precisely the incidence and spectrum of histopathology of cervical cancer in HIV-infected women.

NIH will continue to address the etiology and pathogenesis underlying HIV infection and HIV-associated malignancies through investigations targeting molecular virology, the delineation of the molecular interplay between host and viral gene expressions, and the unique pathobiology of AIDS-related cancers, in particular Kaposi's sarcoma, HPV-related anogenital cancers, and AIDS-related lymphomas.

New initiatives and enhancements have been planned for the Cancer Centers Program in FY 1995 including the development of formal programs within NIH Cancer Centers dedicated to research on HIV-related malignancies, the establishment of a multi-state AIDS/cancer match registry and the creation of a tissue and biologic fluids bank for HIV-associated malignancies that will provide crucial infrastructures for molecular studies. These efforts will facilitate the design of novel agents for the treatment and prevention of HIV-related malignancies. New guidelines for the Cancer Centers Support Grants will encourage the development of pilot projects and feasibility studies in emerging areas of HIV-related malignancy research.

Pathogenic Mechanisms of Disease Progression

Since HIV infection is known to affect the functioning of virtually all the body's organ systems, current basic and clinical research studies are focused on examining the progression of disease in the various systems, including the interactions between HIV and the normal cellular functions of specific cell types. Of particular importance is the study of the effect of HIV infection on various components of the immune system. Studies are examining endocrine alterations associated with HIV infection and AIDS and other effects on the immune system. Additional ongoing studies are examining the effects of HIV infection on the gastrointestinal system, the cardio-pulmonary system, and the central nervous system (CNS). Delineation of the early cutaneous manifestations of HIV infection also is under way and will be expanded.

NIH-sponsored immunopathogenesis research has demonstrated the disabling but non-lethal effects of HIV on macrophages. In addition to direct effects on the cells, HIV may induce factors that inhibit immune function. In this regard, NIH-supported scientists have shown that HIV-infected individuals have elevated levels of an inhibitor called interleukin 1 receptor antagonist (IL-1ra). This receptor antagonist also is produced by white blood cells infected with HIV in cell culture. Increased levels of IL-1ra in HIV-infected individuals may contribute to immune suppression and susceptibility to OIs.

Oral Manifestations

Research continues aimed at isolating and determining the nature of HIV inhibitory factors in saliva, which may explain why HIV can rarely be isolated from saliva and why HIV infection via oral routes is unlikely. Further expansion of HIV-related studies is planned to support research projects aimed at better understanding the pathogenesis of HIV infection including the use of transgenic mice to model the effects of selected portions of the HIV genome. This animal model will be used to explore pathogenic mechanisms as well as therapeutic strategies. Further transgenic mice studies are planned to study clinical manifestations of HIV infection and the role of HIV and host factors in a variety of HIV-related conditions, including nephropathy, psoriasis-like skin lesions, epidermal proliferation in the oral mucosa, growth abnormalities, myopathy, and myositis.

Endocrine Manifestations

Endocrine dysfunction observed as adrenal insufficiency and adrenal disease has been reported in HIV-infected individuals. Thyroid hormone levels in AIDS patients are altered, and thyroid function tests have been found to correlate with survival in acutely ill patients. Moreover, children with HIV infection fail to grow at normal rates, and the role of hormones and growth factors in this growth failure merits evaluation. Other areas of research are targeted to uncovering the metabolic and endocrine basis for the AIDS wasting syndrome and the role of hormones and hormone-like molecules in controlling the function of the immune system.

Wasting Syndrome

The NIH recently has initiated a program to encourage research on the biology of wasting in HIV-infected patients. This new research is based on recent findings that HIV-infected individuals suffering from wasting are most likely to have secondary infections. Research on the role of gastrointestinal immune system and the gastrointestinal and epithelial barriers to foreign agents is essential to understanding, treating, and preventing HIV-infection and its sequelae. Further understanding of gastrointestinal function and nutrition is basic to understanding and treating the wasting syndrome, a major component of HIV-infection that impacts adversely on the immune system and susceptibility to OIs. Research objectives related to wasting include identifying its etiologies, developing parameters for measuring nutritional status of patients, and determining the nonbacterial cause of AIDS-associated enteropathy.

Cardiopulmonary Disorders

HIV-associated heart disease is becoming increasingly recognized as a cause of morbidity and mortality in HIV-infected children and adults. Pulmonary disorders continue to be one of the most frequent medical consequences of HIV infection. Although pulmonary infections, such as bacterial pneumonia and viral pneumonia, represent a major portion of these disorders, a number of interstitial infiltrative processes that cannot be directly linked to a known infectious agent also occur frequently in HIV-infected individuals. A new initiative will support basic research on the etiology, mechanisms of pathogenesis, and host determinants involved in the initiation and progression of HIV-associated lung diseases. An increased understanding of these processes is needed to guide development of effective therapeutic and preventive strategies.

NIH-sponsored studies on the neuropathogenesis of HIV infection are providing important information concerning the neurologic manifestations of the disease, including involvement of both the central and the peripheral nervous systems. Recent studies have demonstrated that HIV infection in the pig-tailed macaque results in histopathologic changes in the CNS that parallel those seen in human AIDS-related dementia. This animal model maybe useful in elucidating mechanisms underlying HIV-induced CNS dysfunction, defining CNS penetration and pharmacology of the dideoxynucleosides and the new protease inhibitors, and assessing neuroimmune destruction accompanying HIV infection.

In FY 1995, NIH will increase its efforts to understand better the neurovirulence of HIV and its role in the neurological impairment that is observed in up to 80 percent of late-stage AIDS patients.

Alcohol Abuse and HIV Infection

Although the relationship between alcohol abuse and infection is widely observed, the mechanisms of interaction between alcohol and HIV infection and the effects of alcohol to further compromise host defenses against infection are not well understood. NIH-sponsored research in this area has focused on alcohol as a cofactor with T-helper cell deficiency to further compromise host immune functions. Results from this research suggest that alcohol abuse increases CNS morbidity associated with HIV infection. In FY 1995, NIH-supported research will continue to investigate the mechanisms of neuropathogenesis associated with alcohol in HIV-infected individuals. Further studies will assess the interactive effects of alcohol and HIV on cognitive, behavioral, and motor impairments associated with various stages of the disease. Investigators will look for correlations between such impairments and neurodiagnostic findings and immunosuppression profiles. In addition, NIH-sponsored research will continue to elucidate the mechanisms and define the parameters that affect the nature and severity of immune dysfunction due to maternal ethanol consumption during pregnancy and lactation.

The effects of illicit drugs on the immune system continue to be studied through NIH-funded research in animal models. Studies will be conducted to determine the effects of illicit drugs, such as opiates, marijuana, and cocaine, and of therapeutics drugs, specifically methadone, LAAM, and buprenorphine, on HIV disease progression. NIH will fund studies to compare progression rates and disease outcomes in drug users, abstinent injection drug users, and residents of drug-free therapeutic communities.

Pathogenesis of HIV-Associated OIs

NIH sponsors research on the pathogenesis of AIDS-related OIs, including tuberculosis, thrush, diarrhea, cryptosporidiosis, herpes, fungal and intestinal pathogens. Computer models also are being developed to simulate the spread of OIs.

NIH will investigate *in vitro* models to evaluate the potential importance of *Mycobacterium tuberculosis* or other mycobacteriosis in HIV-infected individuals in terms of viral replication and disease progression. Additionally, NIH will support studies to elucidate specific mycobacterial gene products involved in human pathogenesis and antibiotic resistance in *Mycobacterium tuberculosis* by using a combination of mycobacterial genetics, enzymology, and animal models. This may lead to potential chemotherapeutic and immunotherapeutic targets for the control of TB.

NIH-funded scientists will continue to conduct research to determine the pathogenesis of the ocular complications of HIV-infection, to identify the risk factors associated with susceptibility to cytomegalovirus (CMV)-retinitis, to develop better diagnostic methods for the identification of ocular HIV-associated OIs, and to develop drugs and drug delivery systems for these conditions. In addition, NIH will support the development of diagnostic methods for the identification of ocular HIV-associated OIs.

NIH will continue a program designed to develop a model of HIV-associated congenital CMV infection to define the role of immunosuppression in maternal-fetal transmission of CMV and the pathological mechanisms of CMV-induced auditory damage. This research also will help define the natural history of CMV infection. Recent work demonstrates that CMV, in a manner similar to that of HIV, is sequestered in various organs (e.g., spleen) when humoral presence of the virus cannot be detected. Sequestered in this way, CMV may replicate like HIV instead of going through a latency period.

HIV Pathogenesis Affecting Special Populations

In response to the changing demographics of the disease, studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents with HIV infection. NIH will continue to support basic research to elucidate the pathogenic mechanisms that may be unique in certain populations.

NIH-sponsored studies will continue to investigate the pathogenesis of anogenital cancers in HIV-infected women in order to define the relationship between human papillomavirus (HPV), HIV, immunosuppression, and anogenital neoplasia. These studies will provide the basis for screening and early detection of premalignant anal lesions in at-risk groups that could lead to prompt treatment to prevent full transformation similar to the way Pap test screening is conducted to prevent cervical neoplasia.

Recent studies have demonstrated that the transmission rate of HIV from mother to infant is between 20 and 35 percent. The NIH will continue to investigate crucial issues associated with maternal-fetal transmission. Research will continue to further delineate the specific mechanisms involved in maternal-fetal transmission; to evaluate whether specific strains of the virus are more likely to be transmitted; to further delineate the role of maternal immunity in prevention of transmission to the fetus; and define the role of cofactors such as substance abuse and other infections; and develop acceptable *in vitro* and animal models of maternal-fetal transmission in humans. Recently, a NIH-sponsored clinical trial has demonstrated that AZT administered during gestation and labor and to the infant after birth reduces the rate of HIV transmission.

In addition, it is important to understand how a woman's use of barrier contraception may affect HIV transmission. Specific research will seek to determine whether vaginal irritation and lesions produced by spermicides in some women increase the rate of HIV transmission. Studies using animal models are crucial to developing spermicides that may be more effective in preventing HIV transmission.

While many of the pathogenic mechanisms involved in HIV infection may be similar for different populations, the timing of HIV infection, expression of OIs, and etiology of CNS complications experienced by women, infants, children, and adolescents may be different from those in men. A major research initiative is planned to identify these pathogenic mechanisms.

Applications of Basic Research

Insight gained from biomedical research studies is crucial for the development of potential therapeutic agents and vaccine candidates that will result in the control, treatment, and prevention of HIV infection and its sequelae. Similarly, the results from etiology and pathogenesis studies of HIV infection and AIDS have major implications for basic biomedical and clinical research in non-AIDS areas. For example, an understanding of the function of the immune system will contribute to increased knowledge of other immune dysfunctions; information concerning the blood-brain barrier will provide the basis for the development of therapeutics for other disorders of the CNS; and the development of targeted drug design strategies will have implications for a wide variety of therapeutics for other diseases. In addition, results from these studies will continue to provide important information for the development of diagnostic assays to preserve the safety of the Nation's blood supply.

AREA OF EMPHASIS:

Therapeutics

Drug Development

The clinical testing of drugs against HIV and HIV-associated OIs and malignancies requires an active preclinical drug discovery and development program. The NIH supports two major approaches in this area: drug screening and rational (targeted) drug development. The screening approach involves the testing of natural and synthetic compounds against HIV and HIV-related malignancies. Rational or targeted drug development involves characterization and delineation of the structural biology of HIV for the purpose of developing agents targeted at inhibiting specific steps in the HIV life cycle.

During the past year, the NIH Preclinical AIDS Drug Screening Program has approved six new drugs for Phase I clinical studies. Approximately 137,000 agents have been screened for anti-HIV activity to date through this program.

To meet the ongoing need for screening large numbers of compounds to identify promising new agents for potential clinical application, NIH will continue to expand the capacity of the AIDS Drug Screen, which currently can conduct up to 72,000 tests per year. The worldwide collection and screening of natural products as sources of unique compounds with novel structures and mechanisms of antiretroviral activity are important to the NIH Drug Screen effort.

Following initial screening, an active compound is further scrutinized for its biological mechanism of action, with particular attention given to which phase of the viral life cycle the compound inhibits. Of special interest are compounds that may act at novel steps in the cycle. Drugs are assayed for their ability to inhibit the activity of specific viral enzymes such as reverse transcriptase (RT) or HIV protease, an enzyme responsible for modifying other HIV proteins in a way that permits production of infectious viral particles. Other tests include analysis of drug metabolism by target cells and identification of HIV activity for the major metabolites. All of these tests are crucial to identifying the most promising compounds for further development.

The National Cooperative Drug Discovery Groups (NCDDG-HIV) and the National Cooperative Drug Discovery Groups for the Treatment of the Opportunistic Infections Associated with AIDS (NCDDG-OIs) have expanded efforts to discover and develop potential treatments for HIV infection and its associated OIs. The Targeted Antiviral Program provides extramural investigators with access to sophisticated techniques, while a similar program has been established for NIH intramural scientists through the Intramural AIDS Targeted Antiviral Program. These programs have resulted in the discovery and development of AZT, ddI, ddC, d4T, and recombinant soluble CD4.

In FY 1995, NIH is planning to initiate the "Special Programs for Innovative Research on AIDS Treatment Strategies" to foster interdependent basic and clinical research based on state-of-the-art research on HIV pathobiology and clinical evaluations of novel therapeutic strategies.

Treatment strategies to be encouraged include innovative approaches to restore or maintain a functional immune system in HIV-infected individuals, and strategies that use macromolecular or cellular mechanisms rather than drug interventions to attack HIV replication directly. Such strategies would include use of genetically engineered cells from the patient or donors to reconstitute the immune system; application of gene therapy to express genes that either protect cells from HIV infection or lead to the death of HIV-infected cells; and other strategies.

NIH is supporting research on using gene therapy to prevent HIV replication. NIH investigators have identified a method to introduce the soluble CD4 molecule into all cells, including those already infected with HIV. Within two months, the previously HIV-infected cells disappear and only healthy, non-infected cells remain. This research may lead to an innovative treatment for HIV-infected individuals using gene therapy.

In FY 1995, the NIH will maintain its support for the Intramural AIDS Targeted Antiviral Program (IATAP) and Protein Expression Laboratory (PEL). The IATAP has developed a facility, with highly sophisticated technologies, that is currently being utilized by 14 ICDs on 50 separate research programs. The PEL produces and purifies various HIV proteins for NIH-wide structural biology studies. The three-dimensional characterization of viral proteins using x-ray crystallography and multidimensional nuclear magnetic resonance are essential for the rational development of drugs that interfere with the virus life cycle by inhibiting the function of various viral proteins. Structure-based targeted drug design programs have achieved progress in determining the structure of several HIV-related molecules, such as RNaseH, p24, and reverse transcriptase. The potential of analogues of these compounds in the treatment of HIV infection and AIDS is currently being studied. New approaches for the development of HIV protease inhibitors are under way. Scientists also are exploring novel molecular strategies to slow or halt HIV replication *in vivo*. One such strategy involves uniquely designed constructs of defective HIV proviral DNA that will target cells expressing HIV envelope protein so as to interfere with viral replication. This type of antiviral therapy could regulate viral replication and reduce viral load, thus delaying progression to AIDS.

NIH also will investigate the reproductive and developmental toxicity of anti-HIV therapies. This effort will investigate the hematologic, neurologic, and specific target organ toxicity of these potential agents in animal models and cell culture systems. In addition, the safety of antiretroviral agents in combination with illicit drugs will be analyzed.

Drug Development and Evaluation of Anti-OI Agents

The NIH, through its intramural and extramural programs, has developed a multifaceted approach for the discovery, development, preclinical, and clinical evaluation of anti-OI drugs. Priority is placed on the identification of effective agents where established therapies do not exist and on the evaluation of new agents with the potential to improve efficacy or reduce toxicities of existing treatment or prophylactic regimens. OIs represent the most common cause of morbidity and mortality of HIV-infected patients.

The increasing incidence of tuberculosis (TB) in HIV-infected populations is a public health priority. A rapid and simple method for evaluating drug susceptibility of *Mycobacterium tuberculosis* has been developed recently by an NCDDG-OI sponsored investigator. The investigator has cloned a luciferase reporter gene. When uninhibited by drugs, such as isoniazid and rifampicin, the mycobacteria glows in the dark. However, when drugs known to kill the organism were added to the culture, emitted light was greatly reduced. This system is envisioned to be capable of screening large numbers of new drugs for improved efficacy, both against sensitive, and multidrug-resistant, strains of *Mycobacterium tuberculosis*.

A recent research advance has occurred in the development of a test to detect *Pneumocystis carinii* (*P. carinii*) in stools from HIV-infected adults and children. Using this test, researchers have produced data which indicates that *P. carinii* may cause persistent diarrheal disease in HIV-infected children. This finding has clinical importance, since *P. carinii* is treatable by a number of therapeutic agents.

NIH sponsors a clinical trials program to evaluate treatments for ocular complications of HIV infection. CMV retinitis, for instance, afflicts approximately 20 percent of HIV-infected individuals and can lead to blindness. In FY 1995, the NIH will further its program for the Studies of the Ocular Complications of AIDS for the development of drugs and drug-delivery systems for ocular complications. In addition, the safety and efficacy of three therapeutic regimens for HIV-related CMV retinitis will be evaluated.

Biomedical research on OIs is challenged by: the limited understanding of the basic biology and natural history of their causative micro organisms; the need for *in vitro* culture systems for susceptibility testing and biochemical studies; the lack of targeted screens or rational design of new agents; the need for optimization of animal models for testing treatment and prophylactic regimens; the need for evaluation of drug combinations for efficacy and safety, drug interactions, pharmacology, and immunotoxicology; and the relatively low level of interest shown by pharmaceutical manufacturers in the development of anti-OIs.

Preclinical and clinical projects are planned for each of the prioritized OIs: *Mycobacterium avium* complex (MAC); Multiple Opportunistic Pathogens Prophylaxis Study (MOPPS), including studies of *Mycobacterium avium, Pneumocystis carinii*, the pathogenic fungi, and *Cryptosporidium;* Wasting syndrome; Cytomegalovirus (CMV) infection; *Toxoplasma gondii* infection; *Pneumocystis carinii* infection; pathogenic fungi infection; and other opportunistic infections.

AIDS-Associated Nervous System Manifestations

Clinical trials continue to focus on the development of increasingly sensitive measurements by which to evaluate HIV-related neurocognitive impairment and any treatment-induced changes in such impairment. Such parameters include the identification of factors predicting changes in neuropsychiatric function and correlation of neuroimaging studies with neurodevelopmental status, HIV activity, and response to antiretroviral therapies. Ongoing neuropharmacologic studies in preclinical animal models and clinical trials in both children and adults will determine the optimal administration of antiretroviral therapies. Planned studies will continue the evaluation of neurotransmitters, neuropeptides, and neurotoxins as markers for HIV encephalopathy and measurements of response to antiretroviral therapies. These may serve as laboratory correlates of drug efficacy in clinical trials involving adults and children. Such factors may play important roles in HIV-induced CNS dysfunction and thus may serve as targets for therapeutic agents. The expansion of studies on the pharmacology and toxicology of antiretroviral drugs with special reference to neurodevelopmental end points will expand the therapeutic regimens against progressive HIV infection. The further development of animal models of central nervous system impairment will permit the evaluation of potential therapies to prevent or ameliorate neurological symptoms associated with HIV infection.

Clinical Trials

The NIH has the primary responsibility for Federally funded clinical trial efforts to evaluate potential therapies for HIV infection and its sequelae. These trials are conducted in the NIAID-funded AIDS Clinical Trials Group (ACTG), the NIAID-funded Terry Beirn Community Programs for Clinical Research on AIDS (CPCRAs), the NIAID-sponsored Division of AIDS Treatment Research Initiative (DATRI), the NICHD-funded sites that collaborate with the Pediatric ACTG, the NEI-funded sites, and the three NIH intramural sites. More than 25,000 patients have been enrolled in these studies, which involve the evaluation of nearly 90 agents.

Accomplishments in NIH-sponsored clinical trials include demonstration of the efficacy and clinical benefits of AZT for adults and children with early and asymptomatic infection; the benefits of ddI in significantly prolonging life with actuarial 2-year survival of 80 percent, even in individuals with advanced stages of disease; the safety and efficacy of ddI for HIV-infected adults and children; the benefits of ddI resulting in expanded approval for patients who have been on AZT for prolonged periods of time; the antiviral activity of interferon and its benefits for reducing Kaposi's sarcoma lesions; the benefits of nimodipine for the treatment of AIDS dementia complex; and the therapeutic benefits of ddC plus AZT combination therapy. In addition, ddI and d4T have been made available through the parallel track/expanded access programs.

Accomplishments in combating HIV-associated OIs include demonstration of the efficacy of atovaquone (566C80) for treatment of *Pneumocystis carinii* pneumonia (PCP) in patients seriously intolerant of trimethoprim-sulfamethoxazole (TMP-SMX); TMP-SMX for prophylaxis of recurrent PCP; aerosolized pentamidine for prophylaxis and treatment of PCP; fluconazole for the treatment of cryptococcal meningitis; foscarnet for the treatment of CMV retinitis; IV gamma globulin for reducing OIs in HIV-infected children with CD4+ counts greater than 200/mm^3; combination of pyrimethamine and clindamycin for toxoplasmic encephalitis; and itraconazole for disseminated histoplasmosis (shown to be more effective with fewer side effects than amphotericin B).

A recent ACTG study evaluated the neurologic symptoms of patients before and during the administration of oral clindamycin and pyrimethamine for treatment of presumed toxoplasmic encephalitis. The outcome of this study suggests that patients who do not show improvement within 10 to 14 days or whose neurological status deteriorates after starting therapy should be considered for other medical tests to identify other causes for the symptoms.

In FY 1995, the NIH will target the evaluation of treatment strategies including those using innovative approaches to restore or maintain a functional immune system in HIV-infected individuals and attacking HIV replication directly through macromolecular or cellular mechanisms rather than drug interventions. Multi-agent combinations will be tested.

Similarly, the development and conduct of clinical trials of agents that can be used safely and effectively in HIV-infected pregnant women is a major research focus. These studies are investigating: whether AZT, hyperimmune anti-HIV immunoglobulin (HIVIG), or passive immunization of the HIV-infected mother can prevent transmission of HIV infection to infants; the role of breast milk in transmitting HIV from mothers to infants; whether various antiretroviral agents alone or in various combinations can slow disease progression in children, the efficacy of several different therapies for treating HIV-associated OIs in children; and the long-term effects of *in utero* exposure to anti-HIV therapies in HIV-infected and uninfected children. A recent NIH-sponsored clinical trial has demonstrated that AZT administered during gestation and labor and to the infant after birth reduces the rate of HIV transmission.

An ongoing study is evaluating hyperimmune anti-HIV immunoglobulin (HIVIG) for the prevention of perinatal HIV transmission. If this agent can be shown to be effective in reducing or eliminating HIV transmission from infected pregnant women to their offspring, the number of pediatric AIDS cases could be reduced.

In addition, NIH will continue supporting a study to elucidate the effects of HIV infection on growth and developmental processes associated with puberty and to elucidate the nature and progression of HIV-infection in teenagers. This knowledge will be used to develop treatment protocols targeted to HIV-infected adolescents.

NIH will expand two areas of research designed to contribute to prolonging the disease-free state in HIV-infected individuals: symptom management and quality-of-life parameters. For example, further research will evaluate the effects of nurse-managed interventions involving nutrition, stress reduction, and exercise programs on physical endurance, perception of physical functioning, well-being, and immune status. Based on current research regarding quality of life and treatment adherence, this program will be expanded to test interventions to improve quality of life in minority HIV-infected women and to promote HIV-related treatment compliance.

AIDS-Associated Tumors

The NIH has developed a program for the evaluation of AIDS-KS—Growth Factors as molecular targets for therapy. In FY 1995, clinical trials will be continued to evaluate an analogue of fumagillin for blocking proliferation of KS cells.

NIH-funded researchers have developed a "lymphoma subpanel" for the evaluation of agents with activity against AIDS-related lymphomas. To date, 500 agents from the primary Cancer Drug Screen have been tested, and 91 have shown selective activity, with data on another 195 currently being analyzed. So far, eight agents showing selectivity in the lymphoma subpanel are being tested in the SCID mouse model to compare their efficacies with the more customary "anti-lymphoma" agents. A priority has been given to expanding the lymphoma subpanel in order to establish and characterize new AIDS-related lymphoma cell lines, develop "mechanism of action" assays, and use these lines for differential drug sensitivity testing in the *in vivo* SCID model.

Participation of Underrepresented Populations

The participation of specific populations in NIH-funded clinical trials reflects the changing demographics of HIV infection and AIDS. Ongoing efforts within the NIH clinical trials programs are designed to ensure participation of women, children, adolescents, IDUs, and minorities who are affected by the pandemic at an increasing rate. Specific activities in this area include implementation of the CPCRA program, which has dramatically increased NIH enrollment of underrepresented minorities and women in HIV therapeutic trials; establishment of Women's Health Committees within the ACTG and CPCRA organizations; provision of supplements to the ACTG for outreach activities toward these populations; awarding of ACTG funds to minority institutions; implementation of institutional evaluations of ACTG and CPCRA sites to ensure participation of underrepresented populations; establishment of community advisory boards for each ACTG and CPCRA site; and recompetition of the adult units of the ACTG that required plans for enrollment representative of the demographics of the population served by the applicant institution.

NIH-sponsored specialists working with adolescents have developed specific guidelines regarding informed consent and participation of HIV-infected adolescents in clinical trials and natural history research. These guidelines provide a framework of unifying principles for Institutional Review Boards to use in evaluating research protocols that focus on or include adolescents. The development of these guidelines will enable more effective inclusion of adolescents in HIV-related research, thus affording adolescents better access to state-of-the-art care and services.

NIH programs also are involved in disseminating the latest AIDS-related information on state-of-the-art therapies, health care, and prevention techniques to domestic and international audiences. New initiatives are designed to provide community-based organizations with easier access to existing AIDS information resources including online databases. Access to existing databases such as AIDSDRUGS and AIDSTRIALS will be enhanced permitting more readily available clinical research information for health care professionals and the community. Technical assistance to community organizations, particularly those serving minority and other underserved populations, will provide materials and expertise to enable these groups.

AREA OF EMPHASIS:

Vaccines

Development

Developing safe and effective vaccines for preventing HIV infection in exposed individuals is a major public health priority in the national and international effort to combat this pandemic. Various strategies to stimulate a protective immune response against HIV are being explored, and efforts are being made to determine which of these strategies offer the most promise for further development. Vaccines also may serve as immunomodulators to improve immune function and diminish disease progression in HIV-infected individuals. In addition, they may prevent transmission from mother to fetus. Several vaccine development approaches currently being pursued include the use of synthetic viral peptides, recombinant products, and genetic recombinant products.

Significance of Antigenic Variation

Basic research on HIV and the immune system provides crucial information required for the development of potential vaccines. These efforts, however, are complicated by antigenic variations of HIV in different geographic regions. Recent findings indicate that there are five major genotypic subtypes (clades) of HIV-1. To date, only one clade has been found in the United States. The development of vaccine "cocktails" capable of eliciting an immune response to several viral strains may be required to protect against HIV infection.

Basic Research Relevant to Vaccine Development

NIH-funded researchers continue to expand knowledge of the immune system that may be important in developing vaccine candidates. These studies have demonstrated that the V3 loop of the virus is the major component of the virus recognized by antibodies that can neutralize infectivity. Similarly, recent studies suggest that cell-mediated immunity involving cytotoxic T lymphocytes (CTLs) may play an important role in preventing infection. NIH-sponsored studies have shown several bacterial vectors, including BCG, *Salmonella*, and adenovirus, to be potent stimulators of mucosal immunity.

In FY 1995, NIH also will continue to support research to strengthen the scientific base necessary for the development of a safe and effective vaccine(s) against HIV infection. NIH will expand its research efforts to delineate the pathogenic mechanisms of HIV infection at the molecular level. Studies will be designed to dissect the mechanisms of cytokine-induced regulation of HIV expression in latently or chronically infected cells; understand the molecular basis for the regulation of HIV gene expression; and develop new approaches to AIDS vaccine development and evaluation.

Animal models using the HIV/chimpanzee and SIV/macaque also will be pursued further. Recent findings have shown that macaques immunized both by intramuscular and oral routes with an encapsulated, whole-inactivated SIV vaccine were protected when vaginally challenged with SIV. This approach may prove to be a significant strategy to protect against vaginal transmission of HIV. The *Macaca nemestrina* (pigtailed macaque) will continue to be utilized in evaluating potential vaccines.

NIH will conduct research on the development and immunologic assessment of gene therapy-based HIV vaccine candidates. Researchers will investigate methods for formulating and delivering effective gene therapy-based HIV vaccines, including the use of tissue-specific promoters. Recent encouraging findings have shown that direct injection of "naked" DNA-encoding HIV antigens may represent a promising approach to eliciting cell-mediated and humoral immune responses *in vivo*. A clinical trial employing this technique to boost the immune response to HIV in HIV-infected individuals is planned.

NIH investigators will continue to focus on designing synthetic vaccine candidates capable of inducing both cellular and humoral immunity. This involves identifying peptide segments of the HIV glycoprotein envelope and HIV enzymes that can induce an immune response. Another approach is the development of genetically engineered, noninfectious HIV mutants against which a protective response can be generated. Once developed, this type of vaccine could be produced in engineered cell lines.

Vaccine Clinical Trials

The AIDS Vaccine Clinical Trials Network has established five AIDS Vaccine Evaluation Units designed to evaluate potential vaccines in Phase I and II trials. Thirteen Phase I and Phase II trials have been initiated to date. Currently, eight vaccine candidates are undergoing evaluation at these sites: six based on gp160 or gp120, one recombinant virus, and one peptide.

Significant progress has been made in the development of potential vaccines for the prevention of HIV infection. For example, all vaccine candidates tested to date in Phase I trials have been shown to be safe and well tolerated. Phase I trials involving HIV-seronegative individuals have shown that the majority of vaccines produce binding antibodies. Titers of neutralizing antibody directed toward homologous virus are low, neutralization titers against heterologous virus also are low or nonexistent, and the duration of the response has varied from weeks to months. In addition, recent studies of a recombinant vaccinia virus gp160 vaccine candidate followed by a booster of a recombinant subunit vaccine candidate have produced functional CTLs capable of destroying HIV-infected cells.

Phase II Clinical Trials

The NIH has initiated Phase II trials of two gp120 vaccine candidates in uninfected at-risk individuals. The NIH also has developed a study protocol and will soon initiate the first Phase II trial of a vaccine candidate in HIV-infected individuals as well as a trial in HIV-infected pregnant women to study the possibility of preventing maternal-fetal transmission. In order to characterize the types of responses obtained to different vaccine candidates, serum samples from vaccines will be evaluated using state-of-the-art techniques.

Infrastructure for Phase III Efficacy Trials

Clinical evaluation of potential vaccines in Phase III efficacy trials is being planned in several domestic and international areas with populations at risk of HIV infection. Through the Preparation for AIDS/HIV Vaccine Evaluations (PAVE) initiative, eight awards were made to ensure that the necessary infrastructure required to conduct vaccine efficacy trials is developed and operational at these international sites. Researchers at the PAVE plan to study cohorts of individuals at risk for HIV infection in order to determine the feasibility of conducting vaccine efficacy trials within these populations. The goal of these studies is to evaluate seroincidence, risk factors, and risk-reduction efforts. These sites may also be used for trails to prevent perinatal transmission. Close collaboration has been established between the PAVE initiative and the NIH AIDS International Training and Research Program (AITRP) to develop necessary infrastructure for international vaccine efficacy trials.

Planned efforts in FY 1995 include: establishment of the HIV Vaccine Efficacy Trials Network (HIVNET) to support domestic and international clinical trial sites; identification of cohorts of at-risk populations for domestic HIV vaccine efficacy trials; development of the infrastructure at the Caribbean Epidemiology Center (Trinidad) as a potential site for vaccine clinical trials; and expand training programs at international sites to ensure the infrastructure necessary to conduct vaccine clinical trials.

AREA OF EMPHASIS:

Behavioral Research

NIH AIDS-related behavioral research activities focused on the assessment of behaviors associated with HIV transmission or those that effect the natural history of HIV infection and its related diseases. Improving measurement of both predictors and outcomes in behavioral and mental health research is a priority. Research sponsored by several NIH Institutes and Centers is aimed at enhancing the effectiveness of existing prevention and intervention strategies and the development of new behavioral strategies. Improving the effectiveness of culturally sensitive educational interventions in different populations at risk of acquiring and transmitting HIV infection continues to be important. In addition, behavioral information on participants in clinical trials of vaccines is essential for understanding the efficacy of such interventions. Another important goal of behavioral research is to determine the manner in which individuals, their families, health care providers, and society perceive and respond to HIV risk and infection. The behaviors of vulnerable and previously neglected groups, including women, adolescents, minorities, runaways, the homeless, the severely mentally ill, and older populations, are especially important.

Psychosocial and Behavioral Aspects of AIDS

A complicated mix of behavioral, social, cognitive, and biologic factors combine to place individuals at increased risk for acquiring HIV infection. Research to discern the interrelationships among these factors is essential to developing effective interventions to prevent the spread of HIV.

The NIH is funding studies that examine how knowledge, attitudes, and beliefs about AIDS and other sexually transmitted diseases affect subsequent behaviors that place individuals at risk for acquiring HIV. Ongoing studies also address the social, cultural, economic, and psychological factors associated with behaviors that place individuals at risk for HIV infection. These studies focus on the decision-making processes that lead to risk-taking versus protective behaviors and factors that facilitate behavioral change.

Improving AIDS prevention programs also is a concern. Researchers are trying to determine what types of motivational or educational interventions are most effective in reducing unsafe sexual behaviors in at-risk populations.

NIH-supported prevention research has demonstrated some key components of successful behavior change intervention and generated important site and population specific data; however, research which tests interventions across multiple populations in diverse geographic settings is needed. The NIH, in collaboration with other Federal agencies, has initiated a multisite, multipopulation prevention trial to identify theory-based interventions that can be readily adopted by public and private agencies. Such interventions can be used effectively to reach persons who continue to engage in at-risk behaviors, especially targeting difficult-to-reach or underrepresented populations, including minorities, IDUs, adolescents, chronically mentally ill individuals, and prison inmates on work-release programs.

A collaborative program between the NIH and the Agency for International Development has been developed to support basic scientific studies on social and behavioral aspects of AIDS in developing countries and to gather information on risk behaviors and behavioral changes related to HIV transmission throughout the life course. The results of the studies ultimately will be used to develop interventions to reduce behaviors that place individuals at risk for transmitting or contracting HIV infection.

In many cases, studies of human behavior are closely linked with biologic studies. The Multicenter AIDS Cohort Study (MACS) is examining the behavioral correlates of disease transmission and progression in more than 6,000 homosexual and bisexual men as well as the neurologic and psychologic abnormalities that result from HIV infection and the behavioral changes that correlate with the incidence of HIV disease. Other epidemiologic cohort studies, such as the Heterosexual AIDS Transmission Study (HATS), also are addressing behavioral issues. These studies examine both biologically induced behavioral changes associated with HIV infection and those that are independent of biologic effects. Investigations into the impact of intervention on behavioral change also have been incorporated into these studies.

HIV-associated neurological changes can affect mental health. Specialized prevention strategies may be required to accomplish behavior change among impaired individuals. Specialized educational programs also may be needed for children with developmental delays. Early detection of AIDS dementia in the 10 to 15 percent of the HIV-infected population that develops this debilitating disorder is needed.

NIH will continue to support several projects investigating the spectrum, frequency, and determinants of risk behaviors that can promote HIV transmission. Surveys, workshops, and conferences will (1) gather critical data in both adult and teen populations to help understand the relationships among patterns of sexual practices, related risk-taking behaviors, and HIV-infection perceptions and beliefs; (2) design specific and effective cultural and sex/age-adjusted targeted interventions that include teaching protective skills; and (3) identify behaviors that are amenable to change and measure those changes over time.

In FY 1995, NIH also will continue studies that: focus on the development and evaluation of new or improved barrier methods and contraceptive options, including the development of condoms from new polyurethane materials; identify and explain associations between alcohol use or misuse and unprotected sexual intercourse; evaluate innovative strategies targeted at sexual behavior and HIV exposure of drug abusers; and further basic research on the determinants of risk behaviors. In addition, research will be supported to identify the determinants and mediators of HIV-related risk behaviors that can be addressed in community-level interventions. Programs in FY 1995 will develop adherence and compliance strategies and link behavioral approaches with ongoing vaccine and treatment efforts.

Injecting Drug Users

The incidence of HIV infection among injecting drug users (IDUs), their sexual partners, and their offspring is increasing dramatically. The NIH has expanded significantly its programs to identify the mechanisms of behavior and behavior change and the prevention of at risk behaviors. Further development of interventions that are age and culture specific will be pursued.

NIH also plans to initiate a research program, in coordination with other appropriate PHS agencies, to investigate various models and strategies linking drug abuse treatment with medical care. These efforts will include clinical trials of medications, with attention to effects on the prevention, incidence, and progression of medical disorders in drug-abusing populations, including the cost-effectiveness of such programs.

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